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THE MODE OF ACTION OF SULFANILAMIDE

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THE problem of the mode of action of antiseptic drugs has always been one of great interest, and it was only natural that with the introduction of prontosil and sulfanilamide, intensive investigations were instituted to determine how these drugs brought about their dramatic effects. In Domagk's original report upon the chemotherapeutic effects of prontosil in experimental hemolytic streptococcal infections in mice, the fact that the drug was effective only in living organisms was stressed, as was also its lack of effect on bacteria in cultures outside the body. This observation has been repeatedly confirmed in respect to both prontosil and its companion azo-dye, neoprontosil.

This divergence between the *in vitro* and *in vivo* activity of prontosil puzzled the earlier observers and led to the formation of certain hypotheses regarding the action of the drug. Levaditi and Vaisman first considered the possibility that the drug activated host defense mechanisms; next that it prevented the formation of capsules, thus rendering the virulent streptococci susceptible to phagocytosis; and finally, late in 1935, that the drug probably acted upon susceptible micro-organisms in a way that lessened their defenses against those of the host. Domagk, on the contrary, held that prontosil *per se* or a conversion product of this drug acted directly upon

susceptible bacteria *in vivo*. In his latest report this observer stated that "the first phase of action consisted always of an attack directly upon the germs, but the microbes were rarely completely destroyed, being more often sufficiently modified to be destroyed by means of the defense mechanism of the host." Thus, according to Domagk, the streptococci in prontosil-treated animals behaved like avirulent streptococci.

Little progress in this problem was made until late in 1935, when the Trefouels, Nitti, and Bovet announced that it was their belief that prontosil broke down in the animal body to triaminobenzene and para-aminobenzene sulfonamide (sulfanilamide), and that they had found the latter compound to be an active chemotherapeutic agent in the control of experimental streptococcal infections in mice. This obviously was an observation second in importance only to that of Domagk, because it showed that the azo linkage was unnecessary for therapeutic activity and provided the needed steppingstone for further investigations of the mode of action of these compounds.

However, as has been pointed out, "to show that sulfanilamide is an effective chemotherapeutic agent is a far call from proving that it is the active component of prontosil." Nevertheless, evidence was soon produced that this might be the case when Fourneau, the Trefouels, Nitti, and Bovet reported that the addition of sulfanilamide to cultures of *Aspergillus niger* delayed the growth of these organisms in Raulin's medium, thus demonstrating for the first time the *in vitro* bacteriostatic activity of sulfanilamide. This observation is the keystone upon which rests the major structure of subsequent work dealing with the mode of action of sulfanilamide and its derivatives. It has been confirmed by numerous observers working with a wide variety of microorganisms.

Another link in the chain of evidence that sulfanilamide was the active molecule in prontosil was the demonstration by Colebrook and his associates and by ourselves that the reduction of neoprontosil *in vivo* or *in vitro* results in the production of a bacteriostatic substance and, as was shown by Fuller, that the effective material liberated both *in vitro* and

in vivo from the neoprontosil molecule in the course of reduction is sulfanilamide.

It is important to point out here that there have been numerous objectors to the theory that prontosil and neoprontosil are active only by virtue of their reduction to sulfanilamide. Domagk opposed this belief, first, because he was unable to find any great difference in the *in vitro* bacteriostatic activity of prontosil and sulfanilamide (an observation at variance with the experience of practically all other observers and due to marked technical differences in the conduct of his experiments) ; second, because he considered that the presence of sulfanilamide in the urine of patients receiving prontosil was no indication that it was the active fraction of the dye compound; and finally, because the liberation of sulfanilamide during the course of prontosil therapy was not proof that it was the active fraction, inasmuch as there were a number of therapeutically active compounds which could not possibly liberate sulfanilamide. This last argument is extremely weak, since no one has claimed that sulfanilamide is the only conceivable active compound.

Although we do not intend to dwell at length upon the relation of chemical structure to therapeutic activity, a few observations are worth mentioning for the light they throw on this subject.

It seems quite likely, as just indicated, that the activity of the azo compounds is dependent upon the destruction of the N=N linkage in the body and the subsequent formation of sulfanilamide. The amino group in benzene sulfonamide compounds must be para to the sulfonamide group. Meta- and ortho-amino compounds are inactive. Substitutions in the amino group of sulfanilamide generally lower the effectiveness of the compound; and, as far as our observations go, the activity of any sulfanilamide derivative containing the NH-R group is dependent upon the splitting-off of the R radical, and the subsequent reversion of the compound to sulfanilamide. (The possible exception to the rule would be the hydroxylamine derivative.) It has also been demonstrated that the para amino group is not necessary for activity, as para-

nitrobenzene sulfonamide is an effective compound. (The stability of this derivative *in vivo* is still a matter of discussion.)

Substitutions in the sulfonamide group (SO_2NH-R) may or may not result in a compound showing a lowered degree of activity. For example, sulfapyridine is a highly effective compound, whereas N(p-aminobenzene sulfonyl)-1, 4-oxazine is practically without activity. As far as is known, most of the compounds resulting from substitutions made in the sulfonamide group are stable and, if active, derive their effect from the whole molecule. In other words, the SO_2NH-R linkage is firm. It has also been demonstrated that the SO_2NH_2 group is not the only active radical and that the S, SO, and SO_2 groups possess varying degrees of activity, provided they are placed para to the amino group. Mayer and Oechslin have shown that sulfur-containing radicals are unnecessary for activity, by demonstrating the chemotherapeutic effectiveness of paranitrobenzoic acid in the treatment of experimental streptococcal infections.

Therefore it can be assumed from what is known that the molecules of sulfanilamide and sulfapyridine, while possibly undergoing oxidative changes in the body (at least according to certain theories regarding their mode of action), do not suffer radical alterations in their chemical structure during their period of activity in the body of the infected host. Hence it is highly likely that the way in which sulfanilamide acts upon susceptible microorganisms is similar to the action of sulfapyridine, the variations being only in the intensity of action.

In discussing the mode of action of sulfanilamide and sulfapyridine, it should be borne in mind that, although their activity appears to be directed solely against the invading microorganism, the recovery of the infected subject seems to entail two factors: the drug factor and the host factor. That is to say, while the drug can bring the infection under control, it requires the coöperation of the host's defense mechanism to dispose of the infectious agent. This statement is in agreement with the conception of those investigators who have

attacked the problem by studying the *in vitro* and *in vivo* effects of these drugs.

Under the heading of the drug factor comes the activity of these compounds in inhibiting the growth of, or possibly actually killing, susceptible bacteria, and their ability to neutralize the harmful effects of the toxic products of certain microorganisms. The host factor represents the response of the body's defense mechanisms, such as antibody production and mobilization of phagocytic cells, to the infection produced by microorganisms that have been altered as a direct result of the drug factor.

At the present time it is possible to select from the welter of conflicting opinions three main hypotheses concerning the manner in which sulfanilamide and sulfapyridine exert their bacteriostatic effect upon susceptible bacteria. The first of these is based upon data which are believed to indicate that oxidative changes, in which molecular oxygen plays a rôle, are responsible for the conversion of sulfanilamide or sulfapyridine into "truly" active compounds.

Early in 1937 Mayer concluded that as sulfanilamide appeared to be less active *in vitro* than *in vivo,* one must postulate the formation of a more active compound in the body. This he claimed must be an oxidation product (the process being brought about by an oxidant in the body). In support of his hypothesis, Mayer cited the frequent appearance of methemoglobinemia in patients receiving sulfanilamide, an occurrence which, according to him, implied the presence of an agent capable of oxidizing hemoglobin. Sulfanilamide would be unable to do this, but its first oxidation product, para-hydroxylaminobenzene sulfonamide, could bring about this change. He next synthesized para-hydroxylaminobenzene sulfonamide and reported that its bacteriostatic activity was about one hundred times that of sulfanilamide *in vitro*. In addition, Mayer stated that other oxidation products of sulfanilamide, such as azoxy, nitro, and nitroso derivatives, were also highly active compounds. Little, however, was done immediately to prove or disprove Mayer's hypothesis because of the difficulties surrounding the preparation of the hydroxyl derivative of sulfanilamide.

About a year after Mayer's report was published, Ottenberg and Fox noted that irradiated dilute solutions of sulfanilamide turned blue. Later they reported that this phenomenon did not occur in the absence of oxygen and that the blue substance could be reduced to a colorless product, thus indicating the existence of an oxidation-reduction system. However, they were unable to demonstrate that the blue substance possessed bacteriostatic activity or that the reduction product was sulfanilamide.

Fox, German, and Janeway studied the effects of the addition of sulfanilamide upon electrode potentials in sterile broth (which were unaffected) and in cultures of hemolytic streptococci. They found that, whereas the electrode potential in such cultures fell rapidly during normal growth, it remained elevated during the time that sulfanilamide was exerting its bacteriostatic effect. In the presence of cysteine, or when air was excluded by sealing the cultures with vaseline, the potential was lowered despite the addition of sulfanilamide, and the bacteriostatic activity of the drug was definitely decreased.

Warren, Street, and Stokinger, unlike Fox and his associates, did observe an elevation of the potential of sterile broth to which sulfanilamide had been added, but they doubted that the drug poised the system at a "critical" E_h. They too found that the electrode potentials of cultures of streptococci fell less rapidly in the presence of sulfanilamide. They noted that when the drug was added to twenty-one-hour-old cultures, a rapid rise in potential occurred, and that under anærobic conditions there was no difference between the potentials of the control and sulfanilamide cultures. The same was true in the presence of cysteine, and in such cultures the bacteriostatic activity of sulfanilamide was reduced to a minimum. These investigators did not reach any definite conclusions as a result of their observations, but suggested that it was possible that sulfanilamide inactivated enzyme systems by attacking sulfhydryl or similar groups which are "normally responsible for the attainment of highly negative potentials."

Two years ago Shaffer advanced the hypothesis that sulfanilamide is oxidized in the presence of hydrogen peroxide,

plus essential catalysts, to an active compound. This product is so strong an oxidant that it destroys catalase, thereby permitting more hydrogen peroxide to accumulate. As a result more and more of the oxidation product of sulfanilamide is formed, until eventually a concentration is reached sufficient to attack all reactive reducing systems of the cell, and bacteriostasis or actual killing of the microorganisms ensues.

The second hypothesis dealing with the mode of action of sulfanilamide was advanced by Locke, Main, Mellon, and Shinn. These observers noted that dilute solutions of sulfanilamide, which had been irradiated with ultraviolet light, possessed the property of inactivating catalase. It has been long known that if catalase is inactivated in ærobic cultures of pneumococci, peroxide accumulates rapidly and may reach a concentration that is bactericidal for the pneumococcal cells. Hence, they reasoned that if sulfanilamide was able to inactivate catalase, peroxide would accumulate, and this factor might account for the bacteriostatic or bactericidal action of sulfanilamide.

They described the mechanism as follows:

> The growing bacterial cell has the power to convert sulfanilamide, presumably through mild oxidation, into a derivative which is a highly active anticatalase. This reaction produces an accumulation of anticatalase in the immediate vicinity of the cell. The streptococcus and pneumococcus, being active producers of hydrogen peroxide, are able to grow only so long as the peroxide concentration can be kept below a critical level by outward diffusion, or destruction . . . in the presence of anticatalase, inactivation of catalase takes place in the zone immediately adjacent to the cell with resultant accumulation of hydrogen peroxide to toxic levels.

In support of this view they brought forth evidence to show that peroxide accumulated to higher concentrations in pneumococcal cultures containing sulfanilamide than in cultures without sulfanilamide, and that if there was a "reduction of the percentage of oxygen in the superambient air of broth cultures of the Type I pneumococcus," the bacteriostatic effects of sulfanilamide were either greatly reduced or altogether prevented. However, they also found that when the oxygen concentration was reduced to below 0.04 per cent

(not even approaching anærobiosis!) sulfanilamide was again a strongly bacteriostatic agent in cultures of pneumococci. They further reported that they had observed chain formation in sulfanilamide-containing cultures of pneumococci and suggested that "the nature of this change is reminiscent of the morphology assumed by the avirulent R. culture phase of the pneumococcus."

Before discussing the third explanation offered for the mode of action of sulfanilamide, we should like to point out that the two hypotheses just discussed are based upon a supposed oxidation of sulfanilamide to an active derivative and that an important point in support of this belief is the claim that sulfanilamide and sulfapyridine are inactive under anaerobic conditions. Hence, if it could be shown that sulfanilamide and sulfapyridine are effective bacteriostatic agents under conditions of strict anærobiosis, this would constitute a definite objection to both the oxidation and anticatalase theories, since both are based upon the assumption that molecular oxygen is necessary for the reaction.

Early in 1937 we demonstrated that the reduction of neoprontosil could be brought about by the addition of an excess of cysteine hydrochloride and that the resulting sulfanilamide was bacteriostatic against the C203 strain of hemolytic streptococci even though marked reducing conditions prevailed in the medium. Later in the same year we described the bacteriostatic effects of sulfanilamide in anærobic cultures of *Cl. welchii.* This latter observation has been confirmed by Sadusk and Manahan.

Recently we have studied the bacteriostatic effects of sulfanilamide and sulfapyridine upon hemolytic streptococci and pneumococci under various conditions of anærobiosis. These tests were conducted with rigid precautions to secure anaerobiosis and in each instance the reduction of methylene blue was used as an indication that an aerobiosis had been obtained. It is evident from the data obtained that the bacteriostatic effects of sulfanilamide upon a strain of Type I pneumococcus and upon the C203 strain of Group A hemolytic streptococci were quite good under anaerobic conditions. When sulfapyridine was used as the bacteriostatic agent there

was no difference between the effects noted under aerobic and anaerobic conditions in the pneumococcal cultures (in the majority of tests sulfapyridine sterilized the cultures irrespective of their oxygen content) and there was only a slight difference when the streptococcus was the test organism.

Regardless of the reason for the disagreement between our results and those of other workers who have studied the effect of anaerobiosis upon the bacteriostatic action of sulfanilamide, the fact that we obtained definite bacteriostasis with sulfanilamide and actual killing with sulfapyridine in the absence of air tends to discredit the concept that these drugs are activated by molecular oxygen. Obviously, if anaerobic conditions prevail, hydrogen peroxide cannot be formed from bacteria, as has been postulated. As a matter of record, our experience is in complete harmony with that of Shinn, Main, and Mellon who found that at concentrations of less than 0.04 per cent of oxygen, sulfanilamide exerted a bacteriostatic effect in cultures of pneumococci.

Another observation that throws light upon the importance of peroxide in the mechanism of action of sulfanilamide was made by Fuller and Maxted, who noted that Type III, Group A hemolytic streptococci as a class fail to produce hydrogen peroxide. It just happens that the strains "Richards" and C203 are Type III hemolytic streptoccocci and have been shown by Fuller and Maxted and ourselves not to produce detectable amounts of peroxide in cultures. Nevertheless, both of these strains have been demonstrated to be very sensitive to the bacteriostatic activity of sulfanilamide. As Fuller and Maxted have stated, these observations constitute "an apparently insuperable objection" to the hypothesis of Locke and his associates.

A third theory dealing with the mode of action of sulfanilamide is based upon the idea that the drug acts on bacteria to prevent them from utilizing the substrate or upon the substrate to prevent it from being utilized by the bacteria. In 1937 we suggested that sulfanilamide brought about changes in the metabolism of the streptococcus and stated that it was our belief that the drug acted directly upon this microorganism. Later in the same year Levaditi advanced

the hypothesis that sulfanilamide combined with the body proteins of the host to form a drug-protein complex which was unassimilable by bacteria. Although Mellon and Bambas stated that the drug had no effect upon the hydrogenase of the pneumococcus for glucose, Barron and Jacobs observed that 0.2 per cent sulfanilamide inhibited to a small degree the oxidation of glucose by hemolytic streptococci and of glucose and lactate by Friedlander's bacilli, and Chu and Hastings reported that 0.66 grams of sulfanilamide "invariably reduced the oxygen up-take" of tissues (rat diaphragm and liver and human blood) as well as of beta hemolytic streptococci, gonococci, pneumococci Types I and II, and meningococci. A concentration of 0.0132 grams per cent was effective only in the case of the meningococcus. These observations pointed to the fact that the drug acted directly upon certain of the metabolic processes of microorganisms.

At about this time Lockwood made an important observation in respect to the mode of action of sulfanilamide. He observed that the addition of small amounts of peptone to human serum cultures of beta hemolytic streptococci definitely decreased the bactericidal and, in some instances, the bacteriostatic effects of the drug upon virulent hemolytic streptococci. This observation led him to suggest "that sulfanilamide prevents the specialized metabolic activity required of invasive organisms" and "that this effect may be achieved through prevention of the utilization of the protein substrate of the organisms." He further showed that peptone had a similar protective effect against the action of sulfanilamide and sulfapyridine upon the pneumococcus in human serum and upon *E. coli* in urine cultures. These observations opened new possibilities for the exploration of the field of the mode of action of sulfanilamide, and pointed the way toward two possibilities: first, that peptone produced the anti-sulfanilamide effect by acting simply as a growth stimulant; and second, that peptone actually contained or was the precursor of a substance which would inactivate the bacteriostatic effect of sulfanilamide.

Dr. Eleanor Bliss and I were very much interested in Lockwood's observations and soon we were able to confirm them.

Our next step was to make a systematic study of the factors involved in the so-called anti-sulfanilamide effect of peptone. In order to do this, we selected *E. coli* as the test organism and used a purely synthetic medium throughout the experiments. We first tested numerous brands of peptones and found that in varying degree all possessed the power of altering the bacteriostatic effects of sulfanilamide upon *E. coli* in the synthetic medium. We then tested the effect of further split products of protein such as proteoses, "Aminoids," etc. All of these substances showed a considerable ability to neutralize the effect of sulfanilamide on the test organism in the synthetic medium. The possibility was next explored that either a single amino acid or combinations of amino acids might exert a similar effect to that noted for the split products of protein. More than a year ago we reported that an amino acid (methionine) inhibited the bacteriostatic effects of sulfanilamide upon *E. coli* in a simple synthetic medium. During the past year we have carefully restudied this whole problem from the point of view of whether or not the anti-sulfanilamide effect of methionine could be attributed directly to growth stimulation or whether it represented a true anti-sulfanilamide effect. After numerous experiments which will be reported in detail shortly, we have come to the conclusion that methionine, while showing slight growth-stimulating effects in certain concentrations, also acts as a true inhibitor of the bacteriostatic effects of sulfanilamide upon *E. coli*.

While this work was in progress, other observations were reported that tended to show that sulfanilamide exerted its effect by interfering with the metabolism of susceptible bacteria. MacLeod noted that, while sulfapyridine did not interfere with the dehydrogenase of the pneumococcus for glucose, it did inhibit the dehydrogenases for glycerol, lactate, and peruvate. In 1939 Stamp made a most interesting observation when he reported that an alkaline extract of a normally sulfanilamide-susceptible strain of hemolytic streptococcus had the property of inhibiting the action of sulfanilamide on the homologous and other strains of hemolytic streptococci when they were grown in Hartley broth. This extract stimulated the growth of streptococci in broth in the absence of sulfanila-

mide. Because of the presence of numerous protein degradation products in the medium, he did not consider that the anti-sulfanilamide factor was an amino acid (unless it was one of the rare amino acids which the organisms ordinarily have to synthesize). Therefore, he concluded that this extract might contain a substance which was an essential part of an enzyme system and suggested that it might be a coenzyme.

Shortly after Stamp's work was reported, Green observed that extracts of *Brucella abortus* yielded a potent growth-promoting factor which possessed a marked ability to eliminate the bacteriostatic effects of sulfanilamide. He also noted that a similar fraction which antagonized the bacteriostatic action of sulfanilamide could be extracted from many other bacteria. Interestingly enough, he did not observe a similar effect from yeast extract, meat extract, casein digest, or in five brands of peptone. Thiamin, nicotinic acid, beta alanine, beta indoleacetic acid, pimelic acid, glutamin, uracil, cysteine, inositol, and biotin were found by Green to be negative for the anti-sulfanilamide factor. Two out of four samples of concentrated liver extract showed a slight anti-sulfanilamide activity. A review of his experiments led Green to interpret his findings as follows: "The conclusion seems warranted that the "P" (for pullulating)-factor catalyzes and sulfanilamide inhibits some fundamental chemical reaction which is intimately concerned with bacterial reproduction." He considered that the reaction might well be enzymic in nature and that the P-factor might play the part of a coenzyme as had been previously suggested by Stamp. Shortly after Green's paper appeared, Fleming stated that he too had found that extracts from a number of different bacteria had an anti-sulfanilamide effect and that he believed this phenomenon was possibly related to Lockwood's observations concerning the effect of peptone.

In April 1940 D. D. Woods reported some extremely interesting observations to the effect that para amino benzoic acid inactivated the bacteriostatic effect of sulfanilamide. In Wood's opinion sulfanilamide produced its effect by interfering with some substance essential for the metabolism of the bacterial cell, and he suggested that para amino benzoic

acid was such a substance. He inferred that under ordinary conditions the required para amino benzoic acid is synthesized by bacteria growing in an adequate medium. Hence, in completely adequate media, sulfanilamide in ordinary concentrations is at best only bacteriostatic, and in so far as certain organisms are concerned is practically ineffective in inhibiting their multiplication. However, in poor media in which the synthesis of this compound is difficult for the microorganisms, sulfanilamide is highly effective as a bacteriostatic agent and may be even bactericidal. Woods suggested that the enzyme reaction involved in the utilization of para amino benzoic acid by the organisms is subject to competitive inhibition by sulfanilamide and that this inhibition is due to a structural relationship between sulfanilamide and para amino benzoic acid. Woods considered that the "Stamp factor" contained para amino benzoic acid, and he himself demonstrated that yeast extracts contained a substance which reversed the inhibitory action of sulfanilamide upon hemolytic streptococci. In a subsequent report, Selbie showed that para amino benzoic acid antagonized the curative effects of sulfanilamide in experimental streptococcal infections in mice, thus revealing that the drug was an effective antisulfanilamide agent not only *in vitro* but also *in vivo*. These observations of Woods and Selbie have been widely confirmed.

Shortly after the appearance of Woods' paper, West and Coburn reported that sulfapyridine modified the normal metabolism of staphylococci and came to the conclusion that under the conditions of their experiments sulfapyridine and nicotinic acid competed for the same position in the coenzyme molecule, so that in the presence of sulfapyridine the organism was unable to form coenzymes, and the activity of certain dehydrogenases was inhibited. If coenzymes were supplied (in the form of highly purified yeast coenzymes), the normal metabolism of the staphylococcus was not modified by sulfapyridine, and growth curves appeared to follow the customary pattern. Dorfman, *et al.*, noted a similar effect from sulfapyridine in respect to its action on the dysentery bacillus.

These concepts of the action of sulfapyridine were in harmony with that of Fildes who stated that according to his theory an antibacterial agent should be capable of either combining with an essential metabolite, thus forming a product devoid of the essential metabolitis function, or of blocking an enzyme specifically associated with the metabolite. In the latter instance one would expect the antibacterial substance to have a chemical similarity to its competitor in the enzyme system. The findings of both Woods, West and Coburn, and Dorfman and his associates were in line with Fildes' theories because of the chemical similarity of para amino benzoic acid to sulfanilamide and of nicotinic acid to sulfapyridine.

MacLeod has recently studied various sources of inhibitor substances for sulfapyridine. He has shown that such substances can be demonstrated in extracts of fresh normal muscle, pancreas, and spleen of certain animals, and that after the autolysis of such tissues the amount of inhibitor substance is greatly increased. Active inhibitor was not present in fresh liver from beef, rabbit, or guinea pig, but was demonstrable in autolysates of such tissues. Normal human urine contained little or no active inhibitor, but upon acid hydrolysis considerable amounts of inhibitor were demonstrated. Inhibitor substances were noted uniformly in pus, but none were found in blood serum. According to MacLeod's findings, in certain species of microorganisms the inhibitor was found in the cells only, whereas in others the inhibitors were present in the culture supernatant, and the cells themselves were quite free.

It is obvious from the observations just recorded that the inhibitor substance first noted by Lockwood and subsequently by Stamp, Green, Woods, *et al.*, is quite widespread in nature and that in its biological reactions in respect to sulfanilamide it closely resembles para amino benzoic acid. However, this latter chemical was not demonstrated in nature until Rubbo and Gillespie reported upon the extraction of para amino benzoic acid in a pure form from Brewer's yeast. It is to be remembered that Woods assumed this compound must be a growth factor for various bacteria. Rubbo and Gillespie next showed that para amino benzoic acid was a definite growth

factor for *Clostridium acetobutylicum* when the organism was grown in a synthetic medium. This observation brought about the reinforcement that was lacking for the acceptance of the views of Woods and Fildes because it definitely proved that para amino benzoic acid was a growth factor for micro-organisms. An interesting corollary observation has recently been made by Ansbacher who reported that a certain type of gray hair produced on the bellies of mice as a result of a deficient diet could be prevented by the addition of para amino benzoic acid to the diet, thus showing that this compound has properties which permit it to be considered a vitamin.

Another problem connected with the mode of action of sulfanilamide and its derivatives concerns the effect of these compounds upon the soluble toxins and the toxic products of various bacteria. Bosse was probably the first to report that the presence of prontosil decreased the hemolysin production of streptococci. This was confirmed by Levaditi and Vaisman, who in addition concluded that prontosil and neoprontosil prevented the *in-vitro* action of streptococcal leucocidin.

However, other observers have failed to demonstrate a neutralizing effect by sulfanilamide or neoprontosil upon the soluble "toxins" of the streptococcus *in vitro*. Thus, while this phase of the question is subject to dispute, there can be little doubt that the findings of King and his associates—which demonstrated that in a 1:1,000 concentration neoprontosil, though not bacteriostatic, did cause a lowering of the hemolytic index of streptococci grown in rabbit plasma. Rabbit red-cell clots are of great interest, especially so since sulfanilamide did not produce this effect.

In 1937 Levaditi and Vaisman reported that the endotoxins of the gonococcus, meningococcus, and *B. aertrycke* could be neutralized *in vivo* by sulfanilamide and certain of its derivatives. Staphylococcal toxin was, on the other hand, unaffected by these drugs. These observations have been confirmed and extended by Carpenter and his associates, who have shown that not only is gonococcal toxin neutralized both *in vitro* and *in vivo* by sulfanilamide, but also the toxins of *Staphylococcus aureus*, *Cl. welchii*, and *Cl. tetani*. They have

also demonstrated that the administration of neoprontosil by the *oral* route (but not when injected parenterally) protected the majority of mice against lethal doses of the toxins of the gonococcus, the hemolytic streptococcus, *Staphylococcus aureus, Cl. welchii,* and *Cl. botulinus.* During the past three years we have attempted at various times to repeat the observations of Carpenter and his associates. So far we have been unsuccessful in confirming the observations of those workers who believe that the sulfonamide group of drugs is capable of neutralizing certain bacterial toxins and endotoxins both *in vitro* and *in vivo.*

In discussing the host factor it must at once be pointed out that there is no experimental evidence that sulfanilamide or its derivatives *stimulate* the activity of the reticulo-endothelial system. The activity of the phagocytes or antibodies is generally a secondary (although in some instances a very important) effect of sulfanilamide therapy.

Domagk remarked upon the essentially normal appearance of the leucocytes in peritoneal exudates from mice which had been infected with streptococci and treated with prontosil. However, it was Levaditi who first pointed out that the phagocytosis of streptococci might play an important part in the recovery of mice infected with these organisms and treated with prontosil. This observation has subsequently been confirmed by almost all those who have studied the effects of sulfanilamide therapy upon the cellular response in animals infected with virulent Group A hemolytic streptococci.

During the past three years we have been very much interested in trying to determine what happens to the infecting microorganisms in animals that have been treated with sulfanilamide and its derivatives. Early in our studies we noted that if the streptococcal peritonitis, which can be produced by the intraperitoneal injection of 1,000 M.L.D. of strain C203, was permitted to develop to a stage in which from one to five coccal units could be seen in an oil-immersion field of the stained peritoneal exudate, and then treatment with sulfanilamide was started, two phenomena were observed. The first was that within two to four hours the multiplication of the cocci in the peritoneal exudates of the treated

animals was definitely retarded; in other words, the drug's bacteriostatic effect became apparent. Secondly, with bacteriostasis, an increase in phagocytosis over that already existing was noted. If treatment was continued, the number of extracellular cocci steadily decreased as phagocytosis increased, until a point was reached when the exudate was free from visible streptococci. In contradistinction to the observation that, although phagocytosis might be quite brisk in the untreated mice, the ingested cocci multiplied within the cells and frequently destroyed them, was the finding that in the treated mice the streptococci did not multiply within the cells and were soon digested by the phagocytes.

The chain of events just described is that noted in mice which received a relatively small inoculum of hemolytic streptococci and in which the infection was allowed to progress naturally for a period of six to eight hours before treatment was started. If, instead of this, the mice are treated on the day before and again one hour before being infected, and the infecting dose is large (about five million organisms), although a moderate degree of bacteriostasis and some phagocytosis may be noted in smears from the peritoneal exudate, the streptococci multiply rapidly and the mice succumb in from twelve to sixteen hours.

However, if the streptococci have been grown for two or three generations in 20 mg. per cent sulfanilamide or sulfapyridine blood broth before being injected into the pretreated and subsequently treated mice, bacteriostasis and phagocytosis of the cocci begin almost at once, and within a few hours the peritoneal exudate is clear of streptococci. In untreated control animals the "pretreated" streptococci quickly regain their natural characteristics and the animals succumb within ten to twenty-four hours. This experiment, when taken in conjunction with the previous series, shows that the prior injection of sulfanilamide or sulfapyridine into mice does not activate the drug, and that pretreatment of the streptococci with the drug makes them immediately susceptible to the effects of the drug when they are injected into mice which have been treated.

If the mouse is deprived of its polymorphonuclear leucocytes, as can be done by the administration of benzene, adequate therapy with sulfanilamide is unavailing; the streptococci multiply slowly and the mouse dies in from three to four days. This indicates that bacteriostasis alone is insufficient and that the presence of the leucocytes is necessary if the infection is to be brought under control.

It might be asked: Do not other host factors, such as the development of antibodies, come into play in the recovery of these mice? As far as anyone has been able to show, they do not. Mice which have recovered from a hemolytic streptococcal infection as a result of sulfanilamide therapy are as susceptible to reinfection with the homologous organism as are normal mice. Hence it seems that in mice the bacteriostatic activity of the drug, coupled with the resulting phagocytosis, is the essential factor in recovery from Group A hemolytic streptococcal infection. In human beings this factor is certainly of great importance, but inasmuch as studies of the immune responses of patients ill with hemolytic streptococcal infections and treated with sulfanilamide have not been reported, we cannot say with certainty that it represents the whole host factor.

A second type of host response is noted in mice infected with virulent pneumococci. We have previously shown that both sulfanilamide and 4:4′ diamino diphenyl sulfone exerted a bacteriostatic effect upon the growth of pneumococci in the peritoneal cavities of mice, and that despite this bacteriostasis little phagocytosis was noted. The pneumococci multiplied at a definitely slower rate in the treated animals than in the controls, but all the mice eventually died. It was also shown that the lack of phagocytosis was not the result of damage to the phagocytic cells, for when conditions were made favorable by injecting type-specific antipneumococcal serum, a wave of phagocytosis was noted.

Buttle had found that mice which survived after being infected with fairly large numbers of pneumococci and treated with the benzylidene derivative of diamino diphenyl sulfone were immune to subsequent infection with the homologous type of pneumococcus. Whitby confirmed this observation

(as we have also) when sulfapyridine was used in the treatment of experimental pneumococcal infections in mice.

It therefore seemed from these observations that the mechanism of recovery, through the agency of drug therapy, differed in experimental pneumococcal and streptococcal infections in mice. A series of experiments designed to furnish evidence upon this question shows that if mice are pretreated with sulfapyridine and then infected with a highly virulent (but sulfapyridine-susceptible) strain of Type I pneumococci, a definite multiplication of the cocci occurs for the first four to six hours. Then (provided the treatments are kept up) a change takes place and, with but a minor degree of phagocytosis, the number of cocci rapidly decreases until practically none can be found in the peritoneal exudate at the end of forty-eight hours. What happens to the pneumococci during this period of decrease is unknown. They may be killed by the drug, but there is no evidence for this assumption. All that can be stated with certainty is that they are not engulfed by the phagocytes. We do know, however, that if treatment is discontinued too soon, the infection will recur promptly and the mice will die, although the peritoneal exudate is free of cocci. Hence it is necessary to continue treatment for about five days if permanent survivals are desired.

If, as with the streptococci, the pneumococci are grown for one or two generations in blood broth containing 20 mg. per cent of sulfapyridine and are then injected into mice which have been pretreated and are treated with sulfapyridine, bacteriostasis begins almost immediately and the cocci slowly disappear from the exudate. Here again the phagocytes do not appear to have a prominent function in the removal of the pneumococci. Also, as in the previous experiment, if treatment is stopped when the exudate is just clear of pneumococci, a recurrence of the infection will almost invariably follow.

It seems quite clear in experimental pneumococcal infections that while the drug is holding the infecting organisms in check, the latter must be acting antigenically to bring about the type-specific immunization of the animal. Hence, if treatment is continued until the animal is well immunized, recov-

ery from the infection is permanent. That this is probably true in human beings also is evident from the observations of Wood and Long, who noted in patients ill with pneumococcal lobar pneumonia and treated with sulfapyridine that, although the therapy might bring about a rapid apparent recovery, recurrences of the infection were to be expected if sulfapyridine was discontinued before a type-specific antipneumococcal antibody appeared in their sera.

It may therefore be stated that the host response to chemotherapy in pneumococcal infections differs in both the experimental animal and the human being from that observed in hemolytic streptococcal infections.

A third type of host response has been observed in mice infected with *Cl. welchii* and treated with sulfanilamide. It was found in these experiments that without pretreatment of the organisms, but with the mice treated thirty minutes before being infected, the bacteriostatic effects of the drug are immediately evident. There is no lag period in the action of the drug in this type of infection. It is also of interest to observe that in the beginning phagocytosis is equal in both the control mice and the treated mice, but that, as time goes on, less phagocytosis is noted in the treated mice—obviously because there are fewer bacilli to be engulfed, owing to the inhibitory action of the drug upon the reproduction of the microorganisms. This, therefore, represents a host response in which no bar to phagocytosis exists in either the treated or control animals, and which clearly demonstrates the bacteriostatic activities of the drug *in vivo*.

It is evident from the experiments just outlined that the nature of the host response is of importance if a clear picture of the mechanism of action of sulfanilamide and its derivatives in the control of infections is to be obtained. Thus far we have been able to demonstrate two main types of host response, In the first, phagocytosis seems to have an important function in finally ridding the animal of the infectious agent, whereas specific antibody production either does not occur or is of minor importance. In the second type of host response, primary phagocytosis is slight, and the drug exercises merely an inhibitory effect upon the infectious agent

until the naturally developing specific immune bodies are able to cope with the infection. A third type of host response may exist in which, though phagocytosis is very important, the primary factor in recovery seems to be the immediate bacteriostatic effects of the drug upon the invading microorganisms.

SUMMARY AND CONCLUSIONS

It seems quite probable from the evidence now available that the chemotherapeutic activity of N=N or NH-R derivatives of sulfanilamide results from the breakdown to the parent compound in the tissues of the infected host. In general the SO_2NH-R linkage is a firm one. Effective sulfonamide compounds act as bacteriostatic and, under certain conditions, as bactericidal agents against susceptible bacteria. Whether or not sulfanilamide or its derivatives have the power of inactivating bacterial toxins is still a matter of dispute. At the present time it has been definitely shown that under certain conditions para amino benzoic acid and methionine can neutralize the bacteriostatic effects of sulfanilamide. It has been suggested that para amino benzoic acid exerts its neutralizing influence as the result of its being in competition with sulfanilamide for a place in certain enzyme systems of susceptible bacteria. The mechanism by which methionine neutralizes sulfanilamide is unknown. It is important to recognize the varied host response to infections if a complete picture of the mode of action of these drugs is to be obtained.

MAN'S BODY AND MAN'S BEHAVIOR[1]

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THE scientifically reliable information we now possess of the structure and dynamic machinery of the human body fills more than a seven-foot book shelf. This is also true in regard to our knowledge of the machinery of the more simple and immediate reactions of man to the external environment, including his fellow men. There is also a vast amount of scientific information as to the various ways by which defective heredity, accidental injury, disease, and aging modify the body of man and his behavior. In the present discussion only fragments of this vast information can be touched on, especially if we are to arrive at the frontiers, and give some attention, not only to the "gaps and guesses" in our information, but also to the question "Where do we go from here?"

Man is an animal. Most people think, or hope, man is something more. At times man behaves as if he were something less. Some day we may actually know. We can at least now agree that man is the kind of animal disclosed by his body structures and his behavior. The skeleton, the muscular, the nervous, the sensory, the vascular, the glandular systems, and the physical-chemical machinery operative in and between these systems are practically the same in man as in the other higher animals. In its broader aspects the machinery for defense against disease is also the same in man as in other species. To be sure there are special immunities and susceptibilities in species, just as there are in the individuals within a species.

By the structure of the body, by the capacity for articulate speech, by fundamental behavior, and by the fact of interfertility, the present human race is one species.

While necessary for life as well as for behavior, we can for the purposes of this discussion, eliminate man's bony system, his vascular system, and his muscular system. To be sure, the dictator screams: "We think with our blood," but even man's "bloody thoughts" involve the brain. We do not think with our blood, nor do we think without it. We have, at least, to give some attention to three other systems of human body machinery: systems that have a profound influence on man's behavior. These are the nutritive system, the ductless gland or endocrine system, and the nervous system.

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The Nutritive System

"An army travels on its belly." So does every man, woman, and child in civil life. While it is true that an average well-nourished adult man can live for some fifty to eighty days without food, and only six to eight days without water, and less than ten minutes without air or oxygen, nevertheless, adequate food and an average normal nutrition is one of the essentials for the average normalcy of the behavior mechanisms, because adequate food and normal nutrition determine in part several essential elements of man's behavior, such as his interest and mental and physical alertness, his physical and mental endurance, his industry, as well as his ability to "take it" from his fellow men. Recall the myriads of after-dinner speeches perpetrated and the few mayhems produced by them. All of these are of prime importance to the individual and of some significance in social behavior. As witnessed the old saying: "The way to a man's heart is by way of his stomach." And as for the female of the species "Say it with candy" probably contains an element of actual physiology.

Our present scientific information on quantitative and qualitative food requirements is indeed significant and so is our understanding of the nature and consequence of the dietary deficiency disease. Unfortunately, this knowledge has not yet reached the common man, or when it does reach him, he may not be in position to do anything about it. While all this is true, let us not forget that this modern knowledge concerning an adequate diet is largely an achievement of the present generation. The physical (and, if you please, the mental) man evolved to his present status in the absence of this knowledge and guided solely by the primitive urges of hunger, appetite, thirst, and whatever nutrients were at hand. And this is certainly true even today of wild life in forests, oceans, and streams. What does the shark, the whale, the deer, and the lion know about calories, adequate proteins, of iron and lime, or vitamin B?

There can be no question of the prime importance of an adequate diet and normal nutrition for the normal behavior of man. When we recall the fact that adequate oxygen in the blood is a *sine qua non,* not only for the efficiency of the skeletal muscles, but also for the work of the brain itself, the very center of our behavior mechanism, that the amount of oxygen in the blood is determined by the amount of iron or hemoglobin in our blood cells; that this, in part, is determined by the amount of iron in our food; it is scarcely necessary to point out that anemia due to iron deficiency in our food is a factor in the behavior of man. The same is true for the iodin in our foods, without which the thyroid hormone cannot be produced; and without thyroid hormone neither the brain nor any other body machinery can grow and function normally. Fur-

thermore, one of the vitamins ("B") is apparently absolutely necessary for the stability, if not the very life, of the nervous system itself, which in all the higher animals is the essential machinery for our adjustments to the external environment.

If the foregoing are actually proven facts, adequate food and normal nutrition become a primary factor, not only in life *per se,* but in our social behavior and our social order. If the repeated statements of the President of the United States "that one-third of our nation is at present ill fed" (in addition to being ill housed and ill clothed) is even approximately correct, this becomes *Problem No. 1* in our national life and national defense. It is not very palatable to our national pride, nor does it "point with pride" to our individual and collective ingenuity, intelligence and resourcefulness to have known this for eight long years and yet about the only things we have attempted in the way of remedy are restricting crop production and killing pigs for fertilizer. I said "we" because in our democracy each individual shares in our collective failure.

Because of the importance that the primitive urge of hunger, appetite, and thirst have played in man's past, we may pause a moment to indicate what is now known regarding the machinery of these urges. Hunger is initiated by powerful contractions of the empty or nearly empty stomach, the esophagus and upper part of the small intestines. These hunger contractions are periodic, and the mechanisms are inherited as these contractions start before birth occurs. Though the consciousness of hunger undoubtedly depends on the cortex of the brain, the initiation of the hunger sensation by contraction of the digestive organs is independent of the cerebrum, except in the way of inhibition through emotions, but these hunger contractions induce changes in the heart and vascular system and in the skeletal motor system regardless of the presence of the cerebrum. The hungry animal (man included) is restless, and displays greater boldness and ferocity until starvation depression sets in. Under more primitive conditions there can be little doubt that the hunger urge drove man to violence, war, and cannibalism.

Less is known about appetite than about hunger, but we know that appetite or the desire for any edible food can be cultivated in all normal people. The only exception is, of course, people in whom certain foods produce sickness. Whether appetite for specific foods are inherited in man is an open question, due largely to the difficulty of conducting conclusive experiments on infants. Experiments on lower animals have indicated that these in some way may select adequate diets as opposed to inadequate diets; that is, if they have choice they will take a diet containing adequate vitamins and leave alone a diet containing no vitamins. Many wild and domestic animals, not usually carnivorous or omnivorous,

will eat bones in times of extra calcium needs of the body. If any such desires or appetites, covering specific dietary needs, are inherited in the human species they seem to be covered up or obscured by the habits of the family forced on the infant in the early months of his life, and later further suppressed by the human habit of cooking, spicing, drying, preserving, and refining our natural foods. Perhaps there is a hint of inheritance of appetite for certain foods, such as vitamins and salts, in the occasional dietary vagaries of pregnant women, when such elements as calcium, phosphorus, vitamins, etc., are needed more than usual for the growth of the young. It is, however, equally clear that appetite is easily an acquired urge, a memory from pleasant experiences with foods, for we can acquire a liking for foods with flavors that have never appeared in nature.

Hunger is an unpleasant sensation of tension referred to the epigastrium. When very strong, hunger resembles muscular pain. Appetite, as a pleasant memory, involves the senses of taste, smell, and vision. Thirst, for water, not for wine, whiskey, coffee or tea, is also referred to the oral end of the alimentary canal, namely, the mouth, the throat, the esophagus, and, under exceptional conditions, the stomach. When the body loses water, or is deprived of water ingestion, the incipient desiccation of the blood and the tissues leads to decreased secretion of saliva and a feeling of dryness in the mouth. These conditions lead to the theory that primary thirst was this feeling of dryness in the mouth. Controlled experiments on man and animals have now shown that the thirst mechanism is much more complicated and involves sensory nerves also in the pharynx, the esophagus, and possibly the stomach. It seems significant that all three of these primary feeding urges: hunger, appetite, and thirst, have their sensory origin in the oral end of the digestive tube.

The Hormone System

With the exception of the ovaries and the testes, all the other ductless glands are necessary for normal function of all the body systems and, hence, for normal behavior. Some of them (the liver, the pancreas, the adrenals, the parathyroids) are necessary; that is, the specific chemicals (hormones) manufactured by these several glands, for life itself. The last fifty years of research in this field has yielded very revolutionary information. We have isolated and chemically identified some of these chemical messengers, these catalyzers and chemical coordinators. We have even made some of them in the test tube. We now have an approximate understanding and some control of many human disorders, thanks to these investigations on man and animals. As you may well imagine, there are still gaps and guesses even here, especially in fundamentals.

The supposed or suspected importance of the liver in man's health and man's behavior is embalmed in our language of long ago in such words as choleric, which implies that man's liver or one of its products, the bile, is responsible for man's hot-tempered, angry, and cantankerous behavior, and also in the numerous would-be "liver remedies" foisted on man even today from "Carter's little liver pills" to "Sal hepatica." Indeed, people who are not deterred by letting speculation run miles ahead of facts, if not contrary to facts, speak of this, that, or the other ductless gland as responsible for the major traits in the personality of an individual. They speak, for example, of an "adrenal type," "pituitary type," or "hyperthyroid type" of individual. This can do no harm, as a poetic and romantic pastime, but it is serious when mistaken for science. At least two of these glands call for special consideration in our discussion, namely, the thyroids and the gonads.

The thyroid gland, through its hormone (thyroxin), is a catalyzer of oxidation, growth, repair, and, hence, function of every tissue in the body. It is a material governor of the speed of living. When this gland secretes too much of this chemical, we lose weight, suffer from insomnia, become excessively fatigued from even moderate efforts, become nervous, unstable, and even insane. On the other hand, too little of the thyroid hormone in the body system spells the opposite: physical and mental depression, physical and mental impotence. Because of the profound place of the thyroid hormone in the life of the nervous system, it is clear that this gland is a conditioner of behavior in a very fundamental sense, that a certain rate of secretion of this hormone is a requisite for the normalcy of the nervous system and hence for normal behavior. We know that a certain minimum of iodin in the diet is necessary for the synthesis of this hormone. We more than suspect that a chemical from the anterior pituitary may regulate the rate of output of the hormone by the thyroid. It appears that none of the other ductless glands work normally when there is too much or too little thyroid hormone secreted. We know that when this hormone thyroxin is entirely lacking, there is chemical castration; the ovaries and the testes gradually die. The rest is largely gaps and guesses.

The ovaries and testes produce the chemicals necessary for the development and life of the secondary sex organs in men and women, and hence for the sex urge and normal sex behavior. In mammals at least, including man, the influence of the gonad hormone in the genesis and maintenance of the sex urge appears to be exerted mainly on the secondary sex organs, and on the pituitary gland, rather than on the central nervous system itself. It is a fact that total absence of the gonad hormones leads to almost if not complete loss of the sex urge. But there

is as yet no good evidence that excess of the gonad hormones intensifies the sex urge. That is to say, satyriasis, nymphomania, rape, etc., are matters of the nervous system, or the social conditioning of the individual, rather than hypergonadism, in the sense that we speak of hyperthyroidism. Of course, the memory of sex experience, like the memory of any other experience, will linger and may have some influence on behavior long after total loss of the gonad hormones from accidents, disease, or aging. Nevertheless, I think that whether rape should be treated by castration rather than punished by imprisonment is still a pertinent question.

The fact that men and women with sufficiently normal gonad hormone mechanisms to beget offspring may abandon or even kill their offspring seems to indicate that individual nervous factors and social experience, rather than gonad hormones, are primary in behavior usually spoken of as love and care of offspring.

The testes and the ovarian hormones appear to have identical effects on the anterior pituitary gland. Despite the similarity in chemical structure of the gonad hormones, their action on the secondary sex organs of the male and the female appears to be largely specific. And yet we are confronted with the puzzling fact that either the testes or some organ in the male produce also some ovarian hormones, and either the ovaries or some other organ in the female also produce some male hormone. This fact may have developmental or evolutional significance only. Here is one of the numerous gaps in our understanding. But the fact itself has led some people to postulate that this is the basis for the individually and socially distressing behavior of homosexuality. I doubt that this is the complete answer, if, indeed, it is even a partial answer.

Perhaps the intensity of the emotion induced by the sex act, together with the dominance of sex matters in literature and art, if not in thought of many if not most normal men and women, are responsible for the ancient and modern myth of "rejuvenation," in the sense that the presence of the gonad hormones in the body delays or prevents the general processes of aging. The saying that men and women are as old as their gonads is just not so. All the facts are to the contrary. Total absence of the gonad hormones have no influence on aging and longevity. The preponderance of matters of sex in literature and art, in song and story, rather than in the individual life of all normal men and women, has rendered the concept of "sin" almost synonymous with the breach of the social sex mores and to considering the other aspects of man's inhumanity to man as less damaging to the character of the individual citizen and less injurious to society.

Space permits only a passing reference to another aspect of what, in my opinion, is a gross exaggeration of the sex urge in the mental life of man, as seen in the cult developed by the late Doctor Freud. According to Freud the gonad hormones, and especially the sensory nerves from the "sexual zones" take dominance, especially in our "subconscious" nervous system, from intrauterine life on, as shown especially by his interpretation of dreams: processes usually more illusive than the Delphian Oracle. By this cult even the simple act of nursing becomes an act of sexual implication. There is something to the concept of the subconscious, but this is not a Freudian discovery. And to my way of thinking, it is scientifically unwise to appoint the mentally unstable, the inadequate and abnormal as head guide to the machinery of normalcy. Is it not possible or probable that in those who exhibit mental unbalance and defective behavior, paralleled with sexual frustration and what have you, there are other and more primary factors in the mental unbalance? So far as I know, complete sexual continence, or celibacy, is compatible with normal mental life and social action.

Again, space permits only the briefest reference to the possible function of the adrenal medulla and its product, adrenalin, in the genesis, intensity, and direction of man's emotions and emotional behavior. There is some evidence that strong emotions, through increased action of the sympathetic nervous systems, lead to increased secretion of adrenalin. But there is little or no reliable evidence that this added adrenalin either inaugurates or intensifies the emotions of joy, fear, anxiety, and hate. It may promote the not unusual behaviors (flight, fight) inaugurated by some of these emotional states, according to findings and postulates by our brilliant colleague, Doctor Cannon. It has been difficult to secure clear data on this problem from the experimental animal. The reason is obvious. Some of these days the proponents and the opponents of the theory of the rôle of adrenalin in the genesis of the intense emotions should have their adrenal glands denervated and then come together and compare notes on their emotions.

The main gaps and guesses in the endocrine system today may be summarized as follows:

(1) We know a great deal about the chemistry and the physiological action of the hormones, but very little about what regulates their rate of secretion.

(2) Also we know very little of the cause or causes of the hypoplasia and the hyperplasia of these important glands.

(3) The normal kidneys are very effective regulators of the composition of the internal environment, the blood, but fail to eliminate excess thyroxin, excess parathyroid hormone, excess

pituitary growth hormone, and also excess insulin. Is this a failure in evolution? Or are we just on the way?

The Nervous System

The structural organization, the nutrition, the chemistry, and the physics of the nervous processes—the reflexes, conditioning processes, and memory appear to be identical in all animals that have developed a distinct nervous system. Nothing specifically new in this system has so far been discovered in man except that his general behavior appears to be less fixed by heredity, or so-called instincts, than is the case of many of the lower animals. We sometimes speak of this as the greater plasticity of the nervous system in man. It is also true that for size of body, man has a much greater cerebrum than any of the other animals; that is, he has a greater quantity and, possibly, a greater complexity of organization of the cerebral cortex. The evidence from man and animals is to the effect that the greater part of memory, social conditioning, and so-called voluntary behavior take place in or involve the cerebral cortex. It is true in man and animals, that deprived of this part of the brain the individual becomes essentially a vegetative automaton, with slight if any capacity to learn by experience, and unable to maintain life except through care of others. Recent investigations have disclosed, however, that with the cerebral cortex presumably intact, destructive injuries to the ancient part of the brain below the cerebral cortex, the hypothalamus, may profoundly alter the disposition and personality of the individual and consequently his behavior. It is reliably reported, for example, that the higher apes with such hypothalamic injuries may change their wildness, viciousness, pugnacity, etc., towards docility. I could name some persons in this and other countries on whom I would like to try this experiment.

This central nervous machinery, the brain, is maintained by chemical elements in the blood and primarily driven by the continuous and occasional messages reaching it from all the sensory nerves of the body, so that when all or most of these sensory impulses are cut off from the brain, we go to sleep. Recent experiments, however, have indicated that certain types of rhythmic activity processes can go on in isolated parts of the central nervous system. The significance of this type of activity in conscious and subconscious behavior is still an open question.

It may be of interest to note that the nervous system, the *sine qua non*, of consciousness, memory, and complex behavior, inherited and developed by experience, has the same lowly origin in evolution as the skin that covers man's body. This is the system whose quality and quantity, whose capacity for memory (that is, persistence of experience) obviously

determines behavior, the happiness and unhappiness, the success and failure of man in health and disease. All this and much more is unquestionably true, but there are still huge deficiencies in our knowledge of this field because, in many cases, we have failed to discover organic or chemical basis in the brain for abnormality in consciousness and behavior patterns.

Conscious phenomena, intelligence, personality, and behavior appear to be just as much an evolution of the material world as is the rest of the body structures and body processes. We seem to be forced to this conclusion from the evidence of the intimate dependence of all phases of consciousness, memory, and behavior on the quantity and quality of the nervous system, and these, in turn, depend on all the rest of the body mechanism. It is perfectly true that we can cut off an arm or leg, remove certain peripheral ganglia and even a certain limited part of the central brain without seriously interfering with consciousness, personality, and fundamental behavior. We can leave the brain structure anatomically intact, and through poisons eliminate consciousness temporarily or alter the individual personality and behavior permanently. The data from brain tumors, brain injuries, drugs (such as sedatives, hypnotics, and anesthetics) experimental physiology, defective heredity show that there is a close correspondence or dependence of consciousness, intelligence, memory, individuality and types of behavior on the central nervous system.

What is personality? I think biologists would agree, today, that one element in personality is heredity, the kind of germplasm with which one is endowed at conception. In the case of man and other mammals the original germplasm is subjected to months of intra-uterine environment. The latter is complex, not simple. Such material factors as the constitution, health, and food of the mother appear to have a very real influence on the constitution of the fetus, and, after birth, such material factors as disease, accidental injuries, food, etc., may further materially modify the final product: man or woman. The hereditary personality is further modified and built up gradually by experience and memory, that is, social conditioning, so that today I am a somewhat different person from what I was twenty years ago. It seems at least highly probable, on the basis of biology, physiology and medicine, that this experience—the cumulative effect of the environment—depends on changes built up mainly in the nervous system. This modification of the nervous system, called memory, is less stable than the hereditary elements of the nervous organization. Disintegration of the nervous system, and changes in behavior may start before the death of the individual. The tragedies of

"second childhood," of the aphasias, of senile dementia are known to all informed people.

The Dominance of the Major Emotional Processes on Behavior

As has been pointed out, we have an approximate understanding of the physiological machinery leading to the development of the conscious states of hunger, thirst, appetite, and the animal sex urge in man. Even more accurate information of the machinery of actual physical pain is available. But there is very little actual information of the machinery involved in the development of the more important conscious states, important in behavior, called fear, greed, affection, dislike, hate, revenge, the awareness of compulsion, the awareness of freedom, and the feeling for beauty. It is known, however, that all of these, and many more conscious mental states, depend for their development and persistence on a relatively normal cerebral cortex and also upon the experience of the individual. The major emotions compete with reason based on facts as drives, or guides, in the behavior of all men. Hunger, the sex urge, greed and hate, are certainly among the most potent drives to action, if not to unsocial action. In their essential nature all of these urges may be classified as uncomfortable, if not unpleasant, mental states from which "action" may bring relief. Most normal people can be conditioned to like a diversity of natural and social environments, unless these are contaminated by too obvious human misery, human depravity and the manifold detritus of man's inhumanity to man. I question the health aspects for man and, hence, the normal behavior of man in large cities, ancient and modern. But our ancestors made out, even in caves. However, they did not have to contend with the other "poisons of civilization."

Normal men and women, even in their prime, act mainly by habit established by experience and not through reasoning. In all normal people conditioning by experience may result in a stereotyped or fixed behavior nearly as predictable as the inherited reflexes, be these simple or complex. The sense or urge for revenge as expressed in the action "An eye for an eye and a tooth for a tooth" may be man's primitive groping for justice. To what extent the machinery for such conscious states as fear, affection, or hate are inherited is still an open question. The physiological expressions in the body of some of these mental states, particularly pain, stimulate complex sub-cortical reflexes, but very likely there is no consciousness of these states either in man or animals, when the cerebral cortex is absent or seriously defective. A very young infant or animal gives expression to fear when suddenly confronted with the unknown. Normal adults may react similarly but, certainly, in most

normal people past early childhood, fear depends on unpleasant experience of the past. Greed, or the desire (and behavior) for personal possession of things to have and to hold, appears early in human infants. It may be one phase of the primitive urge to live. In the adult this mental state is clearly modified by social mores, experience and education.

Psychiatrists speak of "compulsory behavior" in certain forms of mental disorders in otherwise normal people. The major emotions, when sufficiently intense, may actually lead to so-called compulsory behavior in normal men and women. This raises the question of the factual bases for the distinction between compulsory and voluntary behavior in man, that is, the old question of the existence of free choice or the reality and essence of "free will." Perhaps the greater majority of man's ordinary actions are simple or complex responses to various stimuli without the consciousness of choice or the necessity or propriety of choosing entering the conscious states of the individual. Nevertheless, when complex situations face normal people, they do have a *feeling* of choice in their action. I am inclined to think that this feeling of freedom is largely determined by the vagueness of the memory of the past experience which actually determines the choice in any particular case, rather than freedom or "free will" in the sense of behavior without cause. I do not see where this analysis decreases individual "responsibility" for our acts, or puts the onus for the same on society in the abstract. If we knew or understood all about a person's physical heredity, his past and present state of health, the quality of his brain, and *all* about his individual experience and social conditioning, I think the behavior of this individual in any situation could be predicted with a high degree of accuracy. But we do not now have such information about any man.

Perhaps I can make the point more lucid by the following example: recently two men, leaders in a large labor union involved in a serious strike in an important industry, asked to see me. We agreed that under ordinary social conditions: (1) any worker has a right to quit work, that is, strike, (2) any worker has the right to persuade, or try to persuade, a fellow worker to quit work or strike. But we split on the third question, namely, (3) has a worker the right to use physical force in the endeavor to make the other worker quit or to prevent him from returning to work? How do sane men, on the same facts, reach such diametrically different conclusions, conclusions that determine important social behavior? It is clearly not a matter of any known facts, nor of logic or reason. It is also not an instance of "free will" in the usual meaning of that term. It is more likely due to differences in past experience, and the different influence of such experience on the element of wishful

thinking or emotive state of mind that enter into our conception of justice.

Our esteemed colleagues, the philosophers, have had a perennial debate on the question "Is man a rational animal". Is there as yet any evidence of any activity of man that can be labelled "pure reason"? Strict definition of terms and a small dose of the theory of relativity would in all probability terminate this debate, with the following conclusion: The behavior of the average normal man is relatively rational, in the sense of awareness of facts, motives, and "choice," during varying parts of his hours awake. But there is probably nothing like "pure reason" (that is, behavior machinery free from conditioning and affective mental states) in human action.

Well, "where do we go from here"? I am a physiologist, not a prophet. According to the late Professor James there are, still untapped, "lakelets of energy" in the human machinery, ready for more intense if not better human behavior. Maybe so, but I doubt it, as a universal proposition. Wherever we go, the going forward will not be speedy, judging from the rate of man's evolution. It may be too speedy if the path leads down, as a Roman poet put it long, long ago, *"decensus averno facile est."*

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MAN'S CULTURE AND MAN'S BEHAVIOR[1]

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THE scientific basis of anthropology must be established, for anthropology as the theory of culture provides in many ways the scientific basis of all studies concerned with man, his behavior, and his achievements. Culture is clearly the fullest context of all human activities. It is the vast instrumentality through which man achieves his ends, both as an animal that must eat, rest, and reproduce; and as the spiritual being who desires to extend his mental horizons, produce works of art, and develop systems of faith. Thus, culture is at the same time the minimum mechanism for the satisfaction of the most elementary needs of man's animal nature, and also an ever-developing, ever-increasing system of new ends, new values, and new creative possibilities.

An understanding of what this reality is, how it works, how it is constituted and determined, is indispensable for all humanists alike. The archæologist and the historian, who have to reconstruct the past cultural reality from partial data, monumental or documentary, must base their reconstruction on the laws determining the relations between a part and the whole, between economic and juridical phenomena, and between the structure of a society and its creative output. They must be in possession of a scientific theory of culture, or else indulge in more or less inspired, sound, but always intuitive guesswork. In economics and the science of law it is becoming increasingly recognized that the processes of production, exchange, and consumption do not happen in a vacuum, but within a cultural context; while legislation, the behavior of judges and juries, and the effective sanction of legal rules depend upon such factors as public opinion, economic necessities, the level of education, and the type of religion and ethics prevalent in a society. It seems hardly even necessary to stress the fact that the student of contemporary social phenomena and also the psychologist must attack their problems within the real context in which these happen: the context of culture.

Science—to give an unpretentious yet clear definition or reminder—is the translation of experience into general laws which have predictive value. We have to inquire, then, whether it is possible to establish general rules and principles concerning cultural process and product. Such

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rules, to be scientific, must be inferred from observation and be subject to experimental test. They must be generalizations of universal validity. It is essential to have statements of principle which remain true whether applied to primitive or to highly developed culture, to an arctic community or a tropical island tribe in the Pacific. We have to establish clearly determined relations between cultural variables embodied into formulæ of general applicability.

From the slightly different point of view, it can be stated that science establishes order into its particular subject matter by isolating the relevant factors and forces. It will then be necessary to prove that such relevant factors of structure and forces controlling the process do exist in the domain of culture. Such systems of relevant concatination would give us the clue for the observation of a new culture and the means of describing it adequately. They would also provide the common measure for the comparative, that is, theoretical treatment of all phenomena of organized behavior.

The legitimate subject matter of anthropology, as well as of other social sciences, is culture. The experimental approach to this subject matter must be based on direct observation of collective, organized behavior through field work. By field work I mean the study of living communities and their material culture, whether at a low level of development or within our own civilizations. Such study must be guided by the general theory of culture, whereas observation has to be stated in terms of general principle. As in all sciences, so also here, we shall have to inquire whether the final test of applicability through planned social engineering is possible in the case of social studies.

I am purposely omitting from my definition of the scientific approach the test of quantitative approach, the feasibility of mathematical or semi-mathematical formulation. It is clear that wherever phenomena amenable to counting and measuring are considered, the scientific approach would demand this type of operation. Also, in the rare cases where statistics yield sufficient data for curves or equations, these instrumentalities must be used. The general complexity of a subject matter makes it, as a rule, less amenable to quantitative treatment. In all such treatment, grave errors are introduced and increased in any algebraic manipulations whenever entities are counted or computed that are not really identical. The problem, therefore, of identity or of isolation of relevant factors and of their relations is one which must be solved first, and then only can we debate whether mathematical formulations are likely to introduce more clarity or more presumptuous error into our arguments. It goes without saying that in vital statistics, in certain economic transactions, and in the description of technical processes, espe-

cially at higher levels, the quantitative, as well as the mathematical, procedures have been already employed and cannot be left out of consideration.

As regards the primary character of science, that is, the cross-fertilization of observed fact and theoretical argument, the anthropologist has certain initial advantages and can claim certain achievements. Engaged as he is in the study of primitive cultures for which there are no historic records and very little archæological documentation, the anthropologist, by the very nature of his material, was driven into the field. He had to become his own chronicler and to establish perhaps the first laboratory of social science in methodical ethnographic researches in the field. Since observation always implies theory, we find in modern anthropological studies that exchange of inspiration which comes from the simultaneous contact with facts and the striving to subsume them under general principles.

The wide range of cultural diversities was another motive that inspired the scientific bent in modern anthropology. Sound generalization must be derived from comparison and the use of the inductive method, and here again, unless there is some theoretical common measure of comparison, our induction fails.

As regards applications, anthropology has not as yet many achievements to its credit. Nevertheless, it may be said that social engineering presents certain facilities and a degree of viability when it comes to colonial affairs lacking under our own modern conditions. The colonial power has a control, legislative and administrative, over a primitive tribe, far greater than that admissible in a democratic commonwealth. Totalitarian experimentation, again, is not based in its sociological aspect on a scientific policy. In democratic countries, the typical politician is a disturbing link when it comes to the scientific guidance of public events. He is, as a rule, more keen to become a lawgiver than to be amenable to law in the scientific sense.

Obviously anthropology has no claims whatsoever to deal with the scientific problem of culture alone. It had certain initial advantages. To use them fully it must, first and foremost, disclaim some spurious pretenses. The savages are not the only representatives of man. We know full well that modern savagery is as illuminating as its primitive version. Thus, sociology, as soon as it becomes fully infected with the field-work habits of the anthropologist, will have at least quite as much to contribute to the scientific theory of culture as its humbler collaborator. Indeed, in the science of culture we would fail completely as anthropologists unless full cooperation is established between the study

of the human mind, of modern societies and cultures, and of such well-established specialities as jurisprudence and economics.

The Nature of Cultural Process

Considering culture as a whole, that is, at all levels and in any environment, recognition must first be given to its instrumental character. We might survey the organization of an arctic community, a tribe living in the tropical jungle, a horde of lowest primitives, such as the Australian aborigines, and anywhere and everywhere we would find them wielding a body of implements, following rules of behavior, cherishing ideas and beliefs, engaging through all this in activities which integrate into a vast and complex instrumental apparatus. At higher levels of development, in the New World civilizations of Mexico or Peru, in ancient Egypt or in modern Europe, the apparatus and the activities are more highly developed, but the total effect is instrumental and so is every one of the differential phases. Man everywhere is maintained by his culture, allowed to reproduce, as well as instructed and assisted in this, supplied with techniques, knowledge, recreation, art, and religion.

Were one to look more closely at any particular culture, every activity would be found to be related to some organization or other. In each we would find a group cooperating, linked by common interests and a purpose. Members of such a group or institution own conjointly a portion of the environment, some implements or machines, and disposes of a quota of national wealth. They obey prescribed norms of conduct and are trained in particular skills. Through their activities thus normed and implemented, they achieve their purpose or intentions, known to everybody and socially recognized. They also produce an impression on the environment, social and physical; they achieve results which can be revealed through a sociological analysis.

We would find such groups in the homes of the people as family groups and domestic institutions, and that the food supply and the production of goods and implements is the result of such organized cooperative work. The temples and the courts of law are maintained and run by groups of people organized for a purpose, moved by definite motives or values, and having a special function in public life.

This surface impression, dictated by sound common sense, might lead the observer to the statement of a few generalizations. Culture as a whole is an extensive instrumental system of organized activities. It is exercised by a system of related institutions, that is, groups of people united by common interest, endowed with material equipment, following rules of their tradition or agreement, and contributing towards the work of the culture as a whole. The interests that supply the motive power and dic-

tate the tasks of the group are at times physiological, as in food production, domestic life, and defense mechanisms. There are, however, other interests, values, and motives connected with science or with art which transcend any biological determinism. We are thus led to the fuller analysis as to what the drives or motives of human beings are, and also as to the principles and forces of human organization.

As regards the drives, man is obviously an animal; hence his organic needs will always give rise to a permanent biological determinism in all behavior. Men eat, sleep, reproduce, and protect their body from excessive temperature, as well as from physical destruction. There is a minimum of elementary conditions that has to be fulfilled so that the individual organism survives and the group retains its numbers. Even a slight, but progressive, deterioration of the healthy organic state would inevitably lead to cultural extinction.

It is equally important to realize that human beings live not by biological drives alone, but also by physiological drives molded and modified by culture. As regards nutrition, food and its intake are not a mere exchange between man and environment. In a primitive tribe or a civilized community, there is an organized system of production, distribution, storing, and preparing, which provides each member with his meals. Here again, consumption, that is, the intake of food, is fashioned by the taste, taboos, and hygienic rules, which partly limit and partly redirect the normal appetite. Propagation is determined, in its very impulse, by the ideals of beauty and desirability in which the sex impulse integrates with æsthetic, economic, and social considerations. The rules of specific taboo, such as incest and exogamy, as well as of preferential mating, dictate the type of courtship, whereas the production of children is universally defined by the law of marriage. Nor are the results of propagation merely biological. The extensive systems of kinship ties and grouping into clans, so prevalent in primitive communities, are the translation into sociological norms of the results of biological propagation. Bodily exercise is determined by economic labor and by systems of sports, recreational pursuits, or even artistic activities. Thus, man everywhere acts under culturally determined incentives; he submits to the norms prescribed by tradition; he cooperates and pools, or redistributes, the produce of his labor.

There are certain phases in human behavior even more removed from biological fact than those here described. In a primitive tribe there are objects of magical virtues or religious sanctity or economic value: the famous bull-roarers of central Australia, the totemic poles of the northwestern American tribes, or the millstones known from Micronesia. In order to understand the value attached to such objects and the activities

that surround them, it would be necessary to enter a world of mythological antecedents or social and economic conventions. We would have to learn the meaning of the dogmatic principles and see how they are expressed in ritual, or economic transaction, or ethics. To understand why certain people indulge in head-hunting and others practice cannibalism, why in certain cultures valuable objects are produced only in order to be destroyed, would obviously require consideration of the formation of cultural value, of legal principle, as well as the native conceptions of wealth, social ranking, and the realities of magical or religious belief.

Accordingly, man is not merely impelled by hunger and thirst, by love, and the desire to sleep. There are other motives connected with ambition, rank, doctrine, and mythology which establish as powerful incentives for conduct as do those of an innate drive. Instrumentality obtains throughout. In other words, it is always found that a human being is impelled to a specific activity in order to attain a desired end. It is obvious, however, that culture solves not merely the simple organic problems, but creates new problems, inspires new desires, and establishes a new universe in which man moves, never completely free from his organic needs, but also following new ends and stimulated to new satisfactions.

All this does not imply that cultural determinism introduces a mere chaos of relativity in which we would have to resort to the arbitrary biddings of a *deus ex machina* of some specific tribal or cultural genius. We shall be able to give a clear definition and catalogue of the biological needs that are the prime movers of human behavior. We shall also clearly establish what we mean by derived needs or instrumental imperatives. Finally, it will be possible to show that the integrative values, such as ideas, belief, moral rule, are also determined and significant through their relation to culture as a whole. The needs of the organism and the raw materials supplied by the environment are the elements of the primary, or biological, determinism. The indirect cultural situation, however, in which the raw materials are obtained and elaborated and the human organism adjusted imposes new cultural, that is, instrumental and integrative imperatives, which are subject to determinism, hence also to scientific analysis.

The ability to establish and to maintain the cultural apparatus confers enormous advantages on mankind, advantages that consist, on the one hand, in a safer and fuller satisfaction of organic needs; and, on the other hand, in the gift of new impulses and new satisfactions. Culture thus satisfied first the minimum standard of living, that of organic survival. It also adds an increased artificial standard of enjoyment, in which

man reaches what usually is described as intellectual, artistic, and ethical pleasures and satisfactions.

For all this there is a price to be paid in terms of obedience to tradition. Man must submit to a number of rules and determinants that do not come from his organism but from submission to his own artifact and machinery, to cooperation, and to the tyranny of words and other symbols. The oft-repeated opposition as between man and machine, in which man is often described as the slave of his self-produced mechanism, his Frankenstein monster, contains an essential truth. Even when man is not enslaved beyond the limits of real necessity, he becomes permanently dependent on his artifacts, once he has started to use them. Cooperation, the social give and take, implies a determined quota of contribution for which man receives, generally, a larger return, but has to remain bound to his social contract. As regards symbolic tradition, it does not always enslave, but it invariably redirects, limits, and determines human behavior.

The Biological Determinism of Culture

We have seen that the biological determinants appear in every culture and that they are invariably refashioned and intertwined with other motives. The problem arises in what sense is it possible to isolate and define biological determinism? And further, in what way is it related to more complex cultural phenomena? The answer is contained in Figure 1,

A. *Impulse* ⟶	B. *Act* ⟶	C. *Satisfaction*
drive to breath; gasping for air	intake of oxygen	elimination of CO in tissues
hunger	ingestion of food	satiation
thirst	absorption of liquid	quenching
sex appetite	conjugation	detumescence
fatigue	rest	restoration of muscular and nervous energy
restlessness	activity	satisfaction of fatigue
somnolence	sleep	awakening with restored energy
bladder pressure	micturition	removal of tension
colon pressure	defecation	abdominal relaxation
fright	escape from danger	relaxation
pain	avoidance by effective act	return to normal state

Fig. 1. Permanent vital sequences incorporated in all cultures.

in which the main types of biological determinism have been summed up severally and concretely. A set of vital sequences is there listed which, it is maintained, are always incorporated into every culture. The concept of vital sequence means that the central activity or biological act, listed in column B, must be performed regularly and permanently in every culture. This part of the performance is integrally incorporated

into culture, with modifications, to be discussed later, as regards certain prerequisites and the conditions under which it is allowed to happen. The drive, listed in column A, invariably receives a profound modification, different from one culture to another. But although modified, the drive can be determined partly in its physiological character, partly in that it is always connected with the biological act. The items listed in column C are again definable in terms of biological fact: satiation, detumescence, the freeing of the organism of waste matter, the restoration of muscular energy, and the using up of biochemical tensions through muscular exercise and breathing.

The three phases can be defined by the biochemist, the physicist, and the ecologist. The actual intake of air or food; the act of conjugation; sleep, rest, nutrition, or excretion, are clearly defined activities, in which several branches of natural science are interested. Thus, the concept of vital sequence is neither vague nor devoid of substance. It refers to happenings within the human organism as related to physical and cultural environment. However much the drive or satisfaction might be refashioned by culture, both drive and satisfaction must be of such a nature as to lead to the performance of each physiological act, adequate in terms of biology. We see here that the concept of form and function of human behavior is included, since each can be defined in terms of natural science.

The vital sequence is thus the projection of a complex cultural reality onto the physiological plane. We can now also define the concept of basic need over and above that of drive. In each culture there must be systems of standardized arrangements which allow of full, regular, and general satisfaction of all the individual drives. The basic need in its several varieties can, then, be defined as including all individual drives that have to be satisfied so as to keep the organisms of a community in a normal state of healthy metabolism. The non-satisfaction of any or every basic need would imply the gradual biological deterioration of the group, which, if cumulative, would lead to extinction. As regards procreation, the basic need here requires that a sufficient incidence of effective reproduction should occur to maintain the numerical strength of a community. In any culture where celibacy, chastity, vows, abstinences, or castration exceeded restricted numerical limits, we would have a process of gradual extinction. The concept of basic need differs from that of drive, in that it refers to the collective exercise of individual drives, integrated with reference to the community as a whole. The satisfaction of basic needs is predicated with reference to all the organisms, to environmental conditions, and to the cultural setting of the community. It need not be, perhaps, stressed that in the study of cultural

realities, whether through field work or in theoretical analysis, we do not resort any more to our analysis in terms of individual drive, but have to rely on the concept of basic need. The drive → activity → satisfaction analysis contains an abstraction of great importance for the foundations of a sound theory of culture. In actual research, however, we do not meet this abstraction, but are faced always with culturally organized satisfactions of integral basic needs.

Figure 2 summarizes concretely and in a highly simplified manner the basic needs and the cultural responses to them. Its meaning will become clearer in detail as our argument advances. For the present, it is clear that it corresponds to a large extent to the list of drives. Several of them, however, have been compressed into one entry in this figure as, for instance, the need of solid foods, liquids, and intake of oxygen. All these are associated with the process of metabolism. Another important point is that each entry is to be considered as integrally related with reference to need and its linked responses. For, as we already know, in the human species biological motive never occurs in a pure and isolated form. Human beings breathe in closed rooms or caves; they have to combine breathing with rules of politeness or taboo, since human breath is, in some cultures, regarded as sacred and in others as dangerous. Nutrition, propa-

A. *Basic needs:* 1, metabolism; 2, reproduction; 3, bodily comforts; 4, safety; 5, movement; 6, growth; 7, health.

B. *Cultural responses:* 1, commissariat; 2, kinship; 3, shelter; 4, protection; 5, activities; 6, training; 7, hygiene.

FIG. 2. Basic needs and cultural responses.

gation, or bodily comforts occur as formed habits. Human beings eat according to a definite daily sequence. They conjugate in accordance with rules of law and morals, or else against them, and thus under cultural conflict. The need for bodily comforts does not arise in an environmental vacuum and then send off the organism in search of a satisfaction. Savages and more sophisticated beings alike wear clothes, carry out a routine of cleanliness, live in habitations, and warm themselves at some permanent sources of warmth. Thus it is clear that the stream of necessities of motives arising out of each need flows, as it were, parallel to the stream of culturally obtainable satisfactions. In the daily round of life, as well as in the seasonal cycle, the human being normally passes through a routine of instrumental effort and of prepared satisfaction in which biological stimulus and organic effort are not hooked up by *ad hoc*, short-circuited links of desire and satisfaction, but are interwoven into two long chains: one of large-scale organized work on culture and for culture; the other, a systematic drawing upon or consuming of already prepared cultural benefits and goods.

The Instrumental Phase of Human Behavior

To make the last argument more concrete and precise, let us again embody it into a diagrammatic presentation:

Drive (1)—Instrumental performance—Culturally defined situation—Drive (2)—Consummatory act—Satisfaction (meta-physiological).

FIG. 3. Instrumentally implemented vital sequence.

This is obviously a much more accurate and less abstract representation than the vital sequence previously shown (Figure 2). Certain similarities between the two obtain. We are here still dealing with the vital sequence, one which includes a biological activity. There are in culture, as will be seen later, sequences that do not include such a link. In this figure there is a definite linkage in which all the phases are determined by the relationship between a biological drive and its satisfaction.

There are however differences. To be true to the reality of typical culture concatinations, it was necessary to split the drive into two parts. Drive (1) is the instrumental motive, the impulse to take the roundabout way that man follows when he produces or purchases his food, prepares it, and places it on his table. In this he acts to a certain extent like the learning animal in a maze, who has to discover and to use the devices which supply it with food. Sex leads the human animal not to conjugation directly, but to courtship and, in many cases, to marriage. In short, the entire training of the human organism teaches the individual to obtain biological ends through the recognition, appreciation, and the handling of the appropriate means.

Drive (2) represents the culturally determined appetite. Man very often does not eat by hunger, hardly ever by hunger alone. He eats at the right time, the right place, and in the right company. His tastes and values are highly shaped, and even when hungry, he will not touch food defined in his own culture as disgusting, unpalatable, or morally repugnant. "One man's meat is another man's poison": my cannibal friends in New Guinea would have developed a healthy appetite is confronted with missionary steak, but turned away in disgust from my tinned Camembert cheese, sauerkraut, or frankfurters, which latter they regarded as gigantic worms. Again, the impulse of sex which, in animal societies, occurs between any two healthy organisms, is culturally inhibited by such taboos as those of incest, of caste prejudice, and to a lesser extent, by appreciation of rank, class, and professional or racial discrimination. What is a comfortable means of sleeping to an African or a South Sea native would be torture to a pampered Parisian or New Yorker. Nor would our beds, bathtubs, and sanitary arrangements be convenient or even usable to a native from the jungle. Thus there is a

two-fold redetermination of physiological drives. Cultural drive occurs in two forms, and each of them is determined by the tradition in which an organism is trained.

Satisfaction in this series has been modified by an adjective. It appears invariably as a cultural appetite rather than as the satisfaction of a pure physiological drive. Breathing, as carried on by certain European communities within the non-ventilated and heavily modified atmospheres of enclosed rooms, would not satisfy an Englishman accustomed to a superabundance of fresh air. The satisfaction of appetite by food discovered to be unclean ritually, magically, or in terms of what is repugnant in a culture does not lead to a normal state of satiety, but to a violent reaction, including often sickness. The satisfaction of the sex impulse in an illicit or socially dangerous manner produces detumescence, but also conflicts which may lead, in the long run, to functional disease.

Thus culture determines the situation, the place, and the time for the physiological act. It delimits it by general conditions as to what is licit or illicit, attractive or repulsive, decent or opprobrious. Although the act itself, as defined in terms of anatomy, physiology and interaction with the environment, is constant, its prerequisites as well as its consequences change profoundly.

The greatest modification, however, in this new diagram consists in the insertion of the two terms: Instrumental phase—culturally defined situation. The instrumental phase, as we shall see in a closer analysis, is always an integral part of a largely organized system of activities. The instrumentalities of food production would have to be connected with agriculture or hunting or fishing. The storing, preparing, and consuming of food happen in a home or a club or a restaurant. The instrumental phase is also the open door through which such elements of culture as artifacts, norms, and cooperative habits enter as essential constituents of human behavior.

Let us consider any instrumental phase. Primitive fire-making subserves the needs of cooking, warmth, and light. It implies the element of artifact, the knowledge and techniques of friction, and also the appreciation of the value of these objects and activities. In any food-producing instrumental phase we would discover the use of the digging-stick, the hoe, the plough; weapons, nets, or traps; and also the whole system of technique and knowledge, of cooperation and distribution with its legal and customary basis. In every instrumental phase of preparatory activities, the following factors are disclosed: (1) artifacts; (2) normed behavior; (3) organized cooperation; (4) symbolic communication by means of language or other signs. These four cardinal constituents of culture are present in each phase at any level of civilization.

One simple inference occurs immediately: the existence of culture depends upon the mechanisms and activities through which every one of these four constituents is produced and maintained, as well as generally distributed. First, therefore, there must exist in every culture forms or organization through which the material substratum of culture, that is, the body of artifacts, are produced, distributed, and consumed. The economic aspect of a culture is omnipresent.

The norms of behavior have to be known and they have to be enforced. Hence again we can postulate that some mechanisms for the statement, the interpretation, and the sanction of law and order must exist in every community. Accordingly at higher levels there exist everywhere legislative bodies, courts of law, and forces of police. In primitive communities such special institutions may be absent or rudimentary. Nevertheless, the equivalents of codifications, of adjudication, and enforcement are never absent. The essence of custom or norm is that it coordinates behavior; hence it has to be known by all those who cooperate. Many norms curb innate tendencies, define privileges and duties, limit ambition, and circumscribe the use of wealth. There is invariably a tendency to circumvent them. Together with the need of force implied in the imperative of social order, we have in authority a principle which implies the existence of force socially determined and physically implemented. We find everywhere, therefore, the political principle, that is, the socially or culturally determined distribution of force and the right to use it.

Finally, we found that communication, through language and other symbolic means, and the transmission of culture are essential parts of our extended instrumental sequence. Both can be subsumed under the concept of training, insofar as the skills, technical and social rules of conduct have to be implanted in the growing organism and maintained through precept and exhortation. Education, at all levels, can be differentiated into schooling and adult education. Thus the derived need of training or fashioning of the organism for its cultural tasks is one which can be listed as the fourth derived imperative of culture.

1.	2.	3.	4.
The cultural apparatus of implements and consumers' goods must be produced, used, maintained, and replaced by new production.	Human behavior, as regards its technical, customary, legal, or moral prescription must be codified, regulated in action and sanctioned.	The human material by which every institution is maintained must be renewed, formed, drilled, and provided with full knowledge of tribal tradition.	Authority within each institution must be defined, equipped with powers, and endowed with means of forceful execution of its orders.
Economics.	*Social control.*	*Education.*	*Political organization.*

Fig. 4. Table of instrumental imperatives.

Figure 4 gives a condensed presentation of the instrumental needs of culture and of the organized responses to them. We have only to add that the instrumental imperatives have the same degree of cogency as those derived directly from biological needs. We have shown that all vital sequences occur in culture through instrumental implementation. Hence no biological need, that is, no need of the community as a whole, can be normally and regularly satisfied without the full and adequate working of the instrumental responses. These latter constitute together the integral mechanism through which the whole set of basic needs receives its regular flow of satisfaction in every culture. Since even the simplest culture raises the level of the quantitative and qualitative standard of living and thus alienates any human group from the direct hand-to-mouth satisfaction by contact with environment, the breakdown of the cultural machinery would imply at least gradual extinction.

Confirmation of this fact is evident when we look at the evidence of historical facts. A serious breakdown in the economic, political, or legal order which usually also implies deterioration in the systems of knowledge and ethics, leads human groups to disorganization and to the sinking of the cultural level. The breakdown of many simpler cultures under the impact of western civilization and the extinction of many racial groups supply one sample. The ever-recurrent decay of once flourishing cultures, which are then replaced by others or else enter a period of Dark Ages, is another case in point. Even today we are faced with a serious threat to culture, that of total war, which is waged not merely in terms of destruction and physical aggression, but also as economic war against the systems of production and, above all, nutritive maintenance. As propaganda, it aims at the breaking down of moral and social resistance through the sapping of the constitutional principles of organization, both as regards defense and the normal working of institutions.

The Emergence of Culture

A clear definition of the symbolic process is still lacking. Its existence was implied throughout, especially in our statements concerning the codes of human behavior, the rules of conduct, the educational processes which largely consist in verbal instruction, and the inculcation of systems of value.

It will be helpful to turn once more to very simple cultural conditions that are on the borderline between the precultural behavior of man, the animal, and the emergence of truly cultural conduct. From the well-known facts of animal training, which have been now raised to a system of principles embodied in the psychology of stimulus and response, it is

established that apes and lower animals can acquire habits and be taught to use artifacts. It is a fair assumption that precultural man, living under conditions of nature, was led frequently to the instrumental use of material objects. Whenever he was placed, with a fair degree of regularity, under conditions resembling those of an experimental maze in which the rat or the guinea pig is being trained, he probably developed individual habits. An individual habit implies at least the development of a skill, the appreciation of the instrumental value of an object and, finally, the retention of both skill and appreciation. This integral retention, diagrammatically embodied in our presentation of instrumentally implemented series, corresponds to the concept of reinforcement, so fruitfully used by Clark Hull and other contemporary psychologists, as the pivotal principle of animal learning. It is not difficult to see that reinforcement, which means the integral retention by an animal organism of a definite sequence in instrumental activities, contains two concepts of great importance to the student of culture, the concept of symbol and that of value.

Reinforcement, however, accounts only for the formation of habits, that is, of individual acquired types of behavior. As long as habit is not infectious or public, it is not a real unit of culture. Culture begins when the transition between habit and custom is made. Custom can be defined as a habit made public by communication from one individual to others and transferable, that is, capable of being ingrained by one generation on to the next.

We have to introduce two more factors as indispensable prerequisites for the transformation of habits into customs. First, the existence of a group in permanent contact and related on the genealogical principle must be assumed. We have further to assume the existence of means of communication which would make possible discourse and symbolic training. The means of communication, moreover, have to be linked and standardized into traditional statements that can be transmitted from the elder generation to the younger. Thus it is necessary to add two more factors to those previously listed.

And once more we come upon the same list of the cardinal constituents of culture: artifacts, skills, that is, norms of behavior; organized groups; and means of communications, that is, symbols and theoretical systems of precept and value.

The raw materials of both sociability and symbolism can also be assumed as pre-existent to the actual emergence of culture. The long infancy of the human species and the formation of families and of family groups was undoubtedly precultural. These are mere assumptions for which proof need not be given, but which are essentially plausible.

The same condition is evident with respect to the raw materials of symbolism. If precultural man were occasionally driven into developing habits, his behavior was determined by what the modern psychologist calls conditioned stimuli. Finding himself regularly within a context of situation and under the urge of a biological drive with no direct satisfaction, he would resort to instrumental behavior. In this the instrument, a piece of wood or stone, and the association of previous effective activity with this object would provide the cue or the conditioned stimulus to action. The fact that an environmental sign directs the organism to action, is essentially symbolic.

Thus we can say that the artifact itself, the typical context of circumstance, the habitual technique, all these functioned symbolically, as well as instrumentally. It may also be assumed that the example of a performance was an act instilled with demonstrative symbolism. When this is added to such symbolic raw material as the bodily or facial expression of emotions, the deictic or otherwise significant gesture, and the natural sound symbols characteristic of many animal performances, it is apparent that symbolism, as significant direction of activity between one organism and another, may, indeed, must have been, precultural.

This allows us to define our idea of cultural emergence by relating a number of empirically substantial facts. The birth of culture probably occurred as a gradual, maybe age-long, process. It was not the miraculous occurrence of sudden speech or intelligence or invention or social organization. It consisted instead of the all-round systematic and effective integration of the partial increments of cultural behavior. As soon as the use of artifacts, the employment of skills gradually tended to become cooperative; in the measure as cooperation led to the development of significant signs and sounds, entering into concerted work as an integral system of links; and these systems of behavior became fixed into tradition; culture was born. The pervading principle of cultural behavior might perhaps be subsumed under the concept of value.

Value means a deep change in the whole organism, especially, no doubt, in the nervous system. It refers to all those attitudes which make for the retention of habits, the submission to traditional rules, the appreciation of and permanent grip upon material objects, and the adequate action and reaction in terms of an articulate sound or formally determined symbol. This latter aspect became, from the very outset, embodied in systems of theoretical knowledge, of belief, and of mythological or historical tradition.

(*To be concluded in the Winter Issue*)

THE TIME IS NOW[1]

By Elisabeth Achelis
President, The World Calendar Association

THE coming of each New Year turns our thoughts naturally to the calendar and we inevitably wonder why this annual time-keeper is so much more complicated and uncertain than is our daily time-keeper, the clock. We question: "Could not the calendar be made as orderly and stable as our clock-time?" And this is just what The World Calendar Association with its 33 international cooperative committees is endeavoring to do. It is offering to the world a new and better calendar more in keeping with our present needs.

Before describing the new World Calendar let us briefly state some of the drawbacks of our present system under which we are laboring. The chief objection is its changeableness. Years never begin on the same weekday, so that days and dates never agree. The months are so irregular that a silly nursery rhyme must constantly aid us as to their proper length; they have either four or five Sundays, Mondays, or Tuesdays; quarter-years are unequal and the first half-year, too, is shorter than the second half; and the week breaks into the months in a most harum-scarum manner. Our present calendar is so burdened with unnecessary pecularities there is no wonder that it causes constant confusion and uncertainty. For example, this year of 1941 began its career two days later than 1940, so that no accurate comparison with last year or another later year is possible. Complicated tabulations are needed to overcome these difficulties, but even these are faulty as they do not indicate with exactitude whether last January (1940) had four or five Wednesdays or June had four or five Saturdays.

What civilization throughout the world needs is a stable calendar as proposed in the new World Calendar. For this purpose, we take a year of 364 days which is divided into 12 months, 52 weeks of seven days, four equal quarters of 91 days, and two half-years of 182 days. We are thus able to arrange for equal quarters, each containing one month of 31 days and two months of 30 days. Each quarter begins on Sunday and ends with Saturday. Each quarter has three months or 13 weeks or 91 days. A quarter is thus a counterpart of the other three. In the future every day of the year would fall on its given day of the week and each would be uniform with every other year. There exists perfect coordination among the various time-units.

[1] From the *Journal of Calendar Reform*, XI, 1941.

"But what about the 365th day?" readers will say. "One cannot drop this day out of the calendar if it is to keep step with the seasons." And the readers are right about this.

The 365th day is added to the outgoing year immediately at the completed fourth quarter after Saturday, December 30. It is placed on an extra Saturday called Year-End Day and dated Saturday, December 31 (or December Y). In leap years the 366th day follows the completed second quarter and is placed on another extra or double Saturday, the Leap-Year Day, and tabulated Saturday, June 31 (or June L). Both these extra or double Saturdays—one every year and the other added mid-yearly in leap years—are World Holidays. They are the stabilizing days by which the calendar becomes perpetual—every year the same.

Days and dates will always agree in The World Calendar. No longer will they shift as heretofore and a greater sense of tranquillity and security will be obtained in our daily, monthly and yearly plannings. The preparing of budgets, arrangements of club programs and vacational periods, income tax payments and insurance premiums, all will be more easily made. And many other important daily engagements will find their regular places in this new calendar schedule. Thanksgiving, for example, could be placed on the fourth Thursday on a specific date, November 23, avoiding the shiftings between a fourth and fifth Thursday as happened in past years, or the third and fourth Thursday of the recent two years. Christmas would happily fall on Monday, December 25, giving to everyone a welcome three-day week-end. New Year's Day logically comes on the first day of the week, Sunday, with business activities beginning on Monday. School vacations could be more easily planned with the school year closing Friday, June 29, and opening on September 11, a week after Labor Day Monday, September 4.

To accept this type of calendar is easy. In the years when both the old and the new would meet on one and the same day the transition is simple. Such a coincidental day and date is *Saturday, December 30, 1944.* By considering Sunday the 31st in the old almanac as the new Saturday Year-End Day in the new, The World Calendar would begin with Sunday, January 1, 1945.

But how can this be done? The United States, through the President, could call an international conference in 1942, preferably not later than 1943, at which a treaty could be signed and ratified making official The World Calendar on January 1, 1945. Before this is done, however, it is important that individuals, national and private organizations (irrespective of political party, special interest or national prejudice) all work for this common goal and so inform the President. For Time knows no

1941

PRESENT GREGORIAN CALENDAR

FIRST QUARTER

	S	M	T	W	T	F	S
JAN				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
FEB							1
	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	
MAR							1
	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31					

90 days

SECOND QUARTER

	S	M	T	W	T	F	S
APR			1	2	3	4	5
	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30			
MAY					1	2	3
	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
JUN	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30					

91 days

THIRD QUARTER

	S	M	T	W	T	F	S
JUL			1	2	3	4	5
	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	31		
AUG						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
	31						
SEP		1	2	3	4	5	6
	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30				

92 days

FOURTH QUARTER

	S	M	T	W	T	F	S
OCT				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
NOV							1
	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30						
DEC		1	2	3	4	5	6
	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30	31			

92 days

This calendar has 52 weeks and must borrow from another week to complete the year. This causes the calendar to change every year and is responsible for its confusion. Also note varying number of days in each quarter.

PROPOSED WORLD CALENDAR

FIRST QUARTER

	S	M	T	W	T	F	S
JAN	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	31				
FEB				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30		
MAR						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30

91 days

SECOND QUARTER

	S	M	T	W	T	F	S
APR	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	31				
MAY				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30		
JUN						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
							**

91 days

THIRD QUARTER

	S	M	T	W	T	F	S
JUL	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	31				
AUG				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30		
SEP						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30

91 days

FOURTH QUARTER

	S	M	T	W	T	F	S
OCT	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
	29	30	31				
NOV				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30		
DEC						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
							*

91 days

*YEAR-END DAY, December 31 or Y, an extra Saturday (a holiday), follows December 30th every year.
**LEAP-YEAR DAY, June 31 or L, another extra Saturday (a holiday), follows June 30th in leap years.

EACH YEAR DIFFERENT

This calendar is always different from year to year.

The quarters are unequal in length. In leap years the first half-year has 182 days; the second, 184 days.

Each quarter begins and ends on a different day of the week.

Each month begins and ends on a different weekday.

The months have a varying number of weekdays.

Each year begins on a different weekday.

This calendar is unbalanced in structure, unstable in form, and irregular in arrangement.

EACH YEAR THE SAME

This 12-month equal-quarter calendar is good for every year.

The quarters are equal in length.

Each quarter begins on Sunday and ends on Saturday, contains 3 months—13 weeks—91 days.

Month-dates always fall on the same weekdays. Each month has *26 weekdays*—plus Sundays.

Each year begins on Sunday.

Year-End Day and Leap-Year Day, the extra Saturdays, are World Holidays.

This revised calendar is balanced in structure, perpetual in form, harmonious in arrangement.

discrimination; it is universal and affects every man, woman and child. Let us then, every one of us, do our part unstintingly to put into actual operation this simple and orderly measurement of Time.

I like to think of The World Calendar as a perfect system of democracy—a democracy of a newer and better pattern wherein each individual time-unit works in full capacity (neither more nor less) and performs its part freely within its own domain toward achieving a harmonious unity. . . . The World Calendar is thus a great uniter. And because of its newer and better pattern, it is eminently fitting that the United States should now also acclaim this newer and better pattern for our calendar: perfect model of true democracy.

PHYSICISTS IN NATIONAL DEFENSE[1]

In his report to the Governing Board of the American Institute of Physics, Dr. Henry Barton estimated that one out of every four physicists in the United States is working on problems of national defense. The estimated number is 1,400 out of a total of 4,100 physicists who are members of at least one national professional society in physics.

A recent survey of more than 130 universities indicates that, of their total staff of 1,100 professors and instructors of physics, over 100 have recently been called away from their campuses for official defense research projects. At least another 200 have been named consultants or assigned full- or part-time defense tasks at their home institutions. Some fifty graduate students of physics have dropped their studies to accept defense assignments.

In addition, there are approximately 300 physicists in the technical services of the army, navy, air corps and other government departments, mostly full time, and of these at least 250 are at work on problems intimately concerned with national defense. It is estimated that 800 of the 2,500 trained physicists employed in industry are at work on problems related to national defense, and the demands of defense agencies and industries for physicists are greater than can be met.

In industry it is estimated that 2,500 trained physicists are employed, many of them in the research laboratories of large corporations. On the basis of reports received at the institute office, at least 800 of these have gone onto new work programs in line with the needs of national defense. Indeed, if all work designed to improve or speed the production of defense materials and products be counted, the number is greater than 800.

Not only is the supply of physicists being strained, but the output of new physicists is being curtailed. The men who have been called from universities for defense research are often those best fitted to train new research physicists. However, their remaining colleagues are assuming increased teaching loads to keep up the standards of training offered to students.

Unfortunately, the careers of many students are about to be disrupted by the draft. Most of them are unmarried and of draft age. Unless something can be done to keep these much needed students in the graduate schools, the number of men receiving advanced training in physics will drop to less than half of the recent average of 130 per year. What the country needs is to multiply this figure rather than to cut it. Since a thorough training in physics requires three or four years of graduate study, it is nearly impossible to increase the annual increment of good new physicists. Therefore, every effort should be made at least to keep it up.

W. H.

[1] From the *Scientific Monthly*, June, 1941.

AWARDS OF SIGMA XI GRANTS-IN-AID OF RESEARCH — 1941-42

Contributions to the Alumni Research Fund amounting to more than $3,500 have been received during the past four months from approximately 1,000 contributors. This total, the largest the fund has ever received, is far short of the sum needed, since 69 applications for Grants-in-Aid of Research amounting to about $20,000 were received. Impressed by the great need, the Committee of Award (Professor G. N. Calkins, Dr. W. R. Whitney, and Professor Harlow Shapley), meeting at Cambridge July 21, recommended that $5,190 be granted to 33 applicants. This sum is more than $1,600 in excess of the contributions received as stated above. In almost every grant the amount awarded was greatly reduced below that applied for, but even so it was impossible to give any grant to more than half the applicants.

Under the circumstances the National Officers feel that it is desirable to call attention once more to this opportunity to aid directly in promoting research in science: the sole object of Sigma Xi. No deductions are made for expenses; the entire amount contributed goes to research. All contributors of $1.00 or more receive the QUARTERLY for one year; those contributing $5.00 or more will receive, in addition, a copy of either Series I or II of *Science in Progress*. Contributions should be sent to the National Secretary, George A. Baitsell, Yale University, New Haven, Conn.

L. F. AUDRIETH, University of Illinois. $250 for studies on liquid-liquid extraction as a method of separating the rare earths.

R. H. BRUCE, University of Wyoming. $150 for an investigation of the thirst drive by means of diathermal techniques.

L. V. COULTER, University of Idaho. $100 for a study of heats of reaction of the alkali metals.

O. J. EIGSTI, University of Oklahoma. $100 for purchase of optical equipment to be used in cytological studies of the pollen tubes of *Tradescantia occidentalis*.

L. L. EISENBRANDT, University of Kansas City. $100 for a study of age resistance to parasitism.

G. F. FERRIS, Stanford University. $250 to aid in the publication of Series IV of the "Atlas of the Scale Insects of North America."

W. S. GLOCK and R. A. STUDHALTER, Texas Technological College. $150 for a study of the anatomy of growth layers in relation to environmental conditions.

MARY A. GRIGGS, Wellesley College. $250 for chemical studies involved in the study of human lead poisoning.

W. L. HARD, University of Maryland. $100 for a study of the differentiation of the alpha and beta cells in the pancreas.

N. J. HOFF, Brooklyn Polytechnic Institute. $250 to aid in securing apparatus for investigating stress and stability in monocoque cylinders.

RACHEL E. HOFFSTADT, University of Washington. $125 for a continuation of studies on the nature of viruses.

D. L. HOLL, Iowa State College. $250 for aid in securing an apparatus to study twisting moments in thin sector-shaped plates.

CHAO-WANG HSUEH, California Institute of Technology. $250 to aid in studies on the spectrum of hydrogen and deuterium.

N. A. KENT, Boston University. $300 to purchase apparatus for a continuation of studies of the problem of the fine structure of hydrogen alpha.

L. R. KUHN, University of Georgia. $50 for studies on growth and viability of pathogenic enterobacteriaceae.

J. B. LACKEY, U. S. Public Health Service, Cincinnati, Ohio. $50 to aid in illustrating a manuscript on Plankton in the Ohio basin.

J. M. LUCK, Stanford University. $200 to aid in the continuation of work on liver proteins, especially crystalline liver albumin.

C. W. MANN, University of Denver. $100 to secure apparatus for an investigation of thyroid functioning in the white rat.

R. D. MANWELL, Syracuse University. $150 for a continuation of studies on avian malaria parasites.

R. E. Marshak, University of Rochester. $150 for a study of internal temperature of main sequence stars.

E. M. Melampy, Louisiana State University. $100 for studies on caste production in the honey bee.

S. L. Meyer, University of Tennessee. $150 for the purchase of micromanipulator to be used in genetic investigations of certain species of the higher fungi.

G. W. Molnar, Miami University. $150 to secure apparatus for the study of electromotive phenomena of frog skin.

E. P. Mumford, Stanford University. $250 for a continuation of studies on animal and plant distribution in oceanic islands.

R. F. Pitts, New York University. $125 to secure apparatus for an investigation of the functional relationships of the medullary respiratory center.

C. L. Porter, University of Wyoming. $50 for expenses associated with field collecting and study of plants in the Southwest, particularly the genus *Astragalus*.

H. W. Schoenborn, University of Oregon. $140 for a study of nutritional requirements of flagellates under bacteria-free conditions.

R. S. Shankland, Case School of Applied Science. $300 to secure equipment for research on correcting the aberrations of the lenses in the electron microscope.

A. N. Solberg, University of Toledo. $150 for the purchase of a portable cooling unit for a constant temperature bath, for maintaining fish embryos at constant temperature during experimental and embryological studies.

Mary L. Willard, Pennsylvania State College. $100 for purchase of equipment to study optical properties of crystals.

J. A. Wilson, University of Idaho. $150 for photographic equipment to finish a problem on the skull structure of a Permian Amphibian.

R. V. Witter, Harvard University. $200 for aid with expenses of collection of material of the embolomerous Permo-carboniferous amphibian, *Cricotus*.

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(Continued from the Summer Number)

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A. J. Scholl, M.D. (Mayo)
Donna Jean Seaman (University of Washington)
William J. Shaw (Nebraska)
Arthur W. Sheafer (Pennsylvania)
Charles B. Shields (Purdue)
Sidney J. Shipman, M.D. (Michigan)
Horace A. Shonle (Illinois)
Lacey L. Shuler, M.D. (Indiana)
O. W. Silvey (Purdue)
Christianna Smith (Cornell)
E. C. Smith (Ohio)
M. H. Smith (Missouri)
E. R. Smith (Syracuse)
Roy H. Smith (Brown)
Temple C. Smith (Purdue)
Andrew J. Sorensen (Iowa)
Stanwood W. Sparrow (W. P. I.)
L. P. Sperry (Yale)
P. E. Sprague (Ohio)
Burrell Stallard (Kansas)
Kathryn F. Stein (Chicago)
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Alfred Still (Purdue)
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M. J. Thompson (Rensselaer)
John W. Thomson, Jr. (Wisconsin)
R. R. Thomson (Michigan)
E. G. Thomssen (Columbia)
Walter D. Tiegeman (Union)
C. VanEpps (Iowa)
D. G. Vedder (California)
Corydon Wagner (Yale)
W. L. Wallace (Cornell)
Dr. James J. Waring (Colorado)
F. A. Welton (Chicago)
Livingston Wernecke (Washington Univ.)
E. L. West (Cornell)
Anna Kellman Whitchurch (Cornell)
N. D. Whitman, Jr.
Dorothy E. Williams (Columbia)
George J. Willier (Washington Univ.)
Volney C. Wilson (Chicago)
A. M. Wolfson (Wisconsin)
Alexander H. Wing, Jr. (Columbia)
Herman I. Wilson (Pennsylvania)
Frederick A. Wolf (Duke)
Rosalind Wulzen (Oregon)
Clyde C. Younglove (Illinois)
Charles C. Zabriskie (Michigan)

THE FORTY-SECOND ANNUAL CONVENTION

The 42nd annual Convention of the Society of the Sigma Xi is scheduled for 4:00 P.M., Tuesday, December 30, at the Hotel Adolphus, Dallas, Texas. Among the important items of business which the Convention will be called upon to consider are the following:

a. Petitions for charters for the establishment of chapters at Louisiana State University, Utah State Agricultural College, Illinois Institute of Technology, and the University of Hawaii. The formal printed petitions will be distributed to the Chapters in October.

b. Reports of the President, the Secretary, and the Treasurer.

c. Election of the President, Secretary, and Treasurer for the ensuing two-year period; a member of the Executive Committee and a member of the Alumni Committee for a five-year term.

The Nominating Committee this year is composed of Professor F. M. Carpenter, Harvard University, Chairman; Dr. Ernest Carroll Faust, Tulane University; and Dean J. W. Barker, Columbia University.

Chapters may make suggestions direct to the Committee or through the National Secretary.

d. The 20th annual Sigma Xi Lecture will be given Tuesday evening, December 30, by the distinguished astronomer, Dr. Edwin Hubble, of the Mount Wilson Observatory.

INSTALLATION OF THE OBERLIN CHAPTER

The Installation Ceremonies of the Oberlin Chapter of the Society of the Sigma Xi were conducted on March 12, 1941 by Dr. Edward Ellery, National President, and Dr. George A. Baitsell, National Secretary. The initiation and installation proper were preceded by a University Convocation at 11:00 A.M. with an address by President Ellery, and a luncheon. Impressive and dignified installation exercises in the late afternoon were conducted by the National President, assisted by the National Secretary.

Following the dinner given in honor of the national officers, guests, and charter members, an evening lecture was delivered to a large and enthusiastic university audience by Dr. A. J. Carlson of the University of Chicago. Dr. Carlson considered the important problems arising from the extensive use of lead arsenate in insect control.

SIGMA XI NATIONAL LECTURESHIPS—1942

(Requests are to be received by the National Secretary by November 1)

Dr. H. A. Bethe—Department of Physics, Cornell University, Ithaca, N. Y.
"Energy Production in Stars"

The energy emitted by a star in the form of radiation is produced in its interior by transmutations of atomic nuclei. The temperature in the interior can be calculated using a method due to Eddington and is found to lie between 15 and 35 million degrees for most stars ("main sequence"). At such temperatures, protons (hydrogen nuclei) move fast enough to penetrate into other nuclei, overcoming their electrostatic repulsion. In main sequence stars, the energy production is mainly due to the "carbon cycle": a sequence of 6 nuclear reactions between protons, carbon, and nitrogen nuclei. The net result of the cycle is the formation of a helium nucleus out of four protons and two electrons, the carbon and nitrogen nuclei acting only as catalysts. The rate of energy production agrees with observation; the prospective life of the sun is about 10 billion years. Other types of stars will also be discussed.

Dr. P. W. Bridgman—Department of Physics, Harvard University, Cambridge, Mass.
"Some Recent Work in the Field of High Pressures"

In the last few years it has been possible to extend by several fold the range of pressures that can be controlled and measured in the laboratory. The principles of construction of the apparatus which have made this possible will be explained. This involves, in general, some method of automatically supporting the vessel on the outside against the internal pressure. The degree of support may be partial or it may be complete by immersing the entire apparatus in a fluid to which a high hydrostatic pressure is applied. The compressibilities of a number of solids have been determined; volume changes up to as much as 50 percent are found. Polymorphic transition is a very common phenomenon and many examples have been studied. Electrical resistance undergoes changes which, for some substances, may be very large. The mechanical properties of solids, such as strength of ductility may be very appreciably affected.

Dr. H. M. Evans—Department of Biology, University of California, Berkeley, Calif.
"Recent Results from Studies on the Anterior Pituitary"

The anterior lobe of the pituitary body occupies a unique place among the endocrine glands because it appears to be a regulating center for the activities of the other endocrine glands. In addition to this activity, the anterior hypophysis participates in the regulation of certain phases of metabolism. Knowledge in this field is being developed at such a rapid rate that only participants in the field are able to separate fact from fancy and give a summary of securely won results. The Berkeley Laboratory has been actively concerned in investigating the physiology of the anterior pituitary for almost twenty years and has also checked the results of other investigators.

Dr. John G. Kirkwood—Department of Chemistry, Cornell University, Ithaca, N. Y.
"The Structure of Liquids"

Recent experimental and theoretical advances in the study of liquid structure are reviewed. The experimental investigation of molecular distribution in liquids by means of x-ray scattering is described and interpreted from the structural standpoint. The theoretical attempts, based upon statistical mechanics, to correlate the macroscopic properties of liquids with the structure and arrangement of their component molecules are discussed. Special attention is given to the mechanism of the melting process and the relationship of liquid structure to the structure of crystalline solids.

Dr. Lionel S. Marks—Department of Engineering, Harvard University, Cambridge, Mass.
"Modern Power Generation"

The development of industry and of transportation during the past 150 years has been made possible by progress in the generation of power. Progress has been necessary along many parallel lines to further the utilization of power for a multitude of purposes. The initial and continuing drive for greater efficiency has been accompanied by a continuous growth in the power obtainable per unit, an increase in compactness, a reduction in weight, an increase in reliability, and diminution in first cost and in labor and maintenance costs. These developments will be reviewed critically; the future outlook will be surveyed. The possibilities of the gas turbine will receive special consideration.

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Tufts—R. L. Nichols, Pres.; R. L. Carpenter, V.-P.; N. Y. Wessell, Sec.; A. H. Howell, Treas.

Santa Barbara State College—F. T. Addicott, Pres.; Emily Lamb, Sec.; Emily Lamb, Treas.

Catholic Univ. of America—F. O. Rice, Pres.; E. Reinhard, Sec.-Treas.

HARLOW SHAPLEY